

PG Textbook of **PEDIATRICS**

VOLUME **2**
**INFECTIONS AND
SYSTEMIC DISORDERS**

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Volume 2

INFECTIONS AND SYSTEMIC DISORDERS

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Preface

In the last decade, many textbooks of pediatrics have been published in India. However, most were targeted towards undergraduates and general practitioners. The number of students opting for postgraduate courses in pediatrics is on the rise. Currently, most postgraduates in pediatrics augment their knowledge by reading and referencing to textbooks published abroad. Many of the Western textbooks are very detailed and provide an important amalgamation of clinical pediatrics with the major advances in genetics, genomics, physiology, diagnosis, imaging, and therapeutics. However, the “state-of-the-art” on the care of the normal and ill neonate, child, or adolescent as presented in these textbooks differ from that practiced in India or South Asia. While these books provide a detailed description of most disorders seen in children, they unfortunately do not provide both evidence-based medicine and astute personal clinical experiences from India. The focus is missing on the core issues relevant in the Indian context, i.e., growth, nutrition, immunization, development, newborn and adolescent health, and programmatic and social issues in child health. The need for a comprehensive postgraduate textbook, which can be adapted to Indian needs, has been recognized and expressed for some time now.

Rapid strides in medicine and technological advances in biological sciences were witnessed in the last decade. Advances in preventive and therapeutic care have opened new prospects for care of children. However, substantial improvements in quality of life have been limited to those with access to healthcare. Poverty, ignorance, war, bioterrorism, misplaced priorities and the lack of political will have prevented many children throughout the world, benefitting from these significant advances. Despite advances in infectious diseases, newer vaccines and preventive neonatal care, mortality and morbidity continue to be unacceptably high. Our priorities for care of children are often different from the developed world. Also, medical advances and good clinical practice must always be coupled with effective advocacy. These aspects need to be addressed in a postgraduate textbook, as current postgraduates are the future decision makers in our country.

It is our earnest wish and hope that the postgraduate textbook will help to fill the long-felt vacuum. It attempts to provide the essential information that postgraduates throughout India need to capture to effectively address the health problems that our children and youth may face in the times to come. Our objective is to be comprehensive yet concise and reader friendly, embracing both the new advances in science as well as the time-honored art of pediatric practice. Both Indian and international experts in respective fields have provided the details that have been further scrutinized for exposition and usefulness to pediatric postgraduates by a chosen team of eminent academicians. We have liberally included tables, line diagrams, images, clinical photographs, illustrative figures, flow charts and algorithms in the main text. The book is divided into 10 major Parts and further arranged into 51 Sections and Annexures to cover all aspects of postgraduate pediatric curriculum. Themes which have major public health relevance for India are extensively covered. It is almost impossible to cover all pediatric problems with the same degree of detail, and hence a careful balance has been made in the details of description of diseases and their management to the needs of the students, and to keep the book to a manageable size. Summary points “In A Nutshell” are provided at the end of each chapter. Selected recent references—mostly leading articles, reviews and position statements—are provided for more detailed information, if desired by the student or the teacher.

Some kind of overlap is unavoidable in a book of this magnitude, with 725 plus minds working on more than 600 chapters simultaneously. We have strived hard to minimize it. We have also tried our best to keep all the chapters on an even keel despite the unavoidable diversity of disciplines, thoughts, experience, and expressive capabilities of the distinguished authors and section editors, from all over the globe. The book would not have been possible but for the support that we received from these erudite contributors. We are indebted to them for their knowledge, introspection, and judgment during the entire process. Together we have worked hard to produce a compilation that will be helpful to those who desire to learn more about child health in India and thus provide better care for children.

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23.5 Adverse Events Following Immunization

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23.13 Typhoid Fever Vaccines

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40.40 Preventive Cardiology in the Young

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PART VII Infectious Diseases

Section 27 BASIC CONCEPTS

Section Editors Jaydeep Choudhury, Piyush Gupta

Chapter 27.1

Epidemiology of Infectious Diseases

VG Ramachandran, Piyush Gupta

DEFINITIONS

Asepsis Combination of efforts directed at preventing entry of microorganisms into any area of body where they are likely to, cause infection.

Carrier A person or animal that has a specific infectious agent in the absence of a clinical disease. A carrier serves as a potential source for further transmission in the community. *Temporary carrier* state lasts for less than 6 months. *Chronic carrier* state is prolonged and may last lifelong.

Case A person who is identified as having a particular characteristic, such as a disease, behavior or condition. An epidemiological definition of a case is not necessarily the same as the clinical definition. Cases may be categorized as possible, probable and definite, depending on how well a set of specific criteria is satisfied.

Chemoprophylaxis Administration of drugs to prevent infection from (i) occurring in the first place; or (ii) progressing into disease.

Contact Exposure to the source of an infection. Transmission due to direct contact may occur when s in or mucous membranes touch, as in body contact, kissing and sexual intercourse.

Contagious Transmitted by contact or close proximity.

Control Disease control programs aim to lower the incidence of new cases, or reduce the proportion of severe cases through treatment to an acceptably low level, so that the disease is no longer considered a major public health hazard.

Decontamination Process that makes objects safer to be handled; it may reduce but does not eliminate microorganisms on the object.

Disinfection Process that eliminates most but not all disease-causing microorganisms from inanimate objects.

Endemic A disease or infectious agent persistent in a given population; also referred to as a disease with a constant incidence of new cases in the area.

Epidemic It is defined as the occurrence, in a community or area, of cases of a disease clearly in excess to what has been expected. In other words, there is an increase in the incidence of the disease above the endemic level. This is a relative term and would differ from one setting to another (for example, 20 cases of pulmonary

tuberculosis in a particular geographic region in a developed country, where tuberculosis is rare, would constitute an epidemic, whereas a similar situation in India would not be abnormal).

Eradication The extermination of an infectious agent, halting transmission of the infection altogether from a given area.

Hyperendemic A disease that is constantly present at a high incidence or prevalence, and affect all age groups.

Incubation period Time interval between invasion of a susceptible host by an infectious agent and the appearance of the first symptom or sign of the disease. For each organism, there is a characteristic range within which, infecting dose, portal of entry as well as host factors like age and immunosuppression give rise to individual variability.

Infection The condition wherein an infectious agent lives and multiplies in the body of the host. Multiplication of the bacteria which are part of the normal flora of the gastrointestinal tract, respiratory mucosa, etc., is generally not considered an infection. On the other hand, multiplication of certain pathogenic bacteria (e.g., *Salmonellae*) is considered an infection even if the person is asymptomatic.

Infection, Iatrogenic Physician-induced infection resulting from some form of intervention, e.g., drug therapy, diagnostic procedures, etc.

Infection, Cross When a new infection from a patient or a healthy carrier establishes itself in an already diseased person.

Infection, Primary It is the very first or the initial infection caused by an infecting organism. Subsequent infection by the same organism is called re-infection. When host resistance is diminished by a pre-existing infectious disease, a new microorganism sets up an infection, which is called secondary infection.

Infection, Nosocomial Cross infection acquired in a hospital. Now known as hospital associated infection (HAI).

Infection, Airborne A disease that is caused by an infectious agent capable of being transmitted by particles or droplets suspended in the air, e.g., measles and whooping cough.

Infection, Atypical Infection where the typical or characteristic clinical symptoms and signs of a particular disease are lacking.

Infection, Endogenous Infection derived from the person's own microflora.

Infection, Exogenous Infection derived from extraneous source, e.g., another human being, environmental source or animal (zoonoses).

Infection, Inapparent or Subclinical An infection that does not cause any detectable clinical signs and symptoms.

Infection, Latent Following an infection, some pathogens may remain in dormant form in host tissues and proliferate only when host resistance is lowered, producing clinical disease.

Invasion The process by which bacteria, animal parasites, fungi and viruses enter the host-cells and spread in the body.

Isolation Separation, for the period of communicability, of infected persons or animals from others in such places and under such conditions as to prevent or limit the direct or indirect transmission of the infectious agent from those infected to those who are susceptible or who may spread the agent to others.

Non-pathogen A microorganism that does not cause disease, but may be a part of the normal flora.

Notifiable disease A disease that by statutory requirements must be reported to the public health authorities.

Outbreak Two or more related cases in infections, suggesting the possibility of a common source or transmission between cases.

Pandemic A worldwide epidemic or an epidemic occurring over a very wide area.

Pathogen A microorganism capable of causing disease.

Pathogen, Opportunistic A microbe capable of causing disease only when the host resistance is compromised.

Pathogenesis Mechanism by which a pathogenic agent produces disease.

Pathogenicity The ability of an infectious agent to cause disease.

Period of communicability The period during which the infectious agent may be passed from a case to other persons in the population, or from an animal to man or vice versa. In some infections, asymptomatic, temporary or chronic carriers may also pass an infection to susceptible persons (e.g., typhoid bacilli).

Reservoir The natural habitat of an infectious agent, where the infectious agent may survive or multiply. It may be human, animal or the inanimate environment such as soil.

Sporadic A disease or event that occurs infrequently and irregularly. Resultant cases are not related to other cases or infection.

Sterilization Elimination of all microorganisms from an object including spores and vegetative forms.

Transmission The spread of an infectious agent, either through the environment or from person to person. The main mechanisms of transmission are direct contact, placental, fomite-borne, vector-borne and airborne.

Vehicle The term is used for inanimate sources of infection, e.g., food, water or fomites.

Zoonosis An infectious disease that is transmitted naturally from vertebrate animals to human beings.

SPREAD OF INFECTION

A communicable disease develops due to the transmission of an infectious agent or its toxic products from an infected person, animal or reservoir to a susceptible host—either directly or indirectly through an intermediate plant or animal host, vector or the inanimate environment (**Box 1**).

Communicable diseases may occur sporadically or in the form of an outbreak. Their incidence is directly related to the general well-being of the society. In developed nations, many of the communicable diseases are rarely seen. However, sexually transmitted diseases and acute respiratory infections are ubiquitous in their occurrence.

Etiological Agents

Bacteria

They cause diseases by (a) invading the tissues or the bloodstream and multiplying in a part of body, which is normally devoid of bacteria; (b) producing a toxin, which might act locally, or at a body site which is far from the site of bacterial multiplication and toxin production; or (c) causing a hypersensitivity reaction, e.g., group A beta hemolytic streptococci causing rheumatic fever or acute glomerulonephritis.

BOX 1 Steps in the spread of an infectious disease

The development or spread of an infectious disease presupposes the presence of the following:

1. An *etiological agent* responsible for the disease should be present
2. There should be a *reservoir* of the etiological agent
3. The infecting agent should be able to escape from the reservoir of infection, through the *portal of exit*
4. There should be a *possible portal of entry* to transmit the agent from the reservoir to the new host
5. The agent should be *able to invade* the tissues of the new host
6. The host receiving the infecting agent should be *susceptible* to the infection.

Virus

These are very small organisms and contain protein encapsulated genetic material which could either be DNA or RNA. The virus attaches to a cell in the human body and then releases its genetic material inside the cell. This genetic material of the virus subjugates the host cell and diverts its normal function in a variety of ways. The host cell can now only produce more and more of virus particles, which invade new cells.

Fungi

These are cellular structures of the plant kingdom. These exist either as yeast (which reproduces asexually by budding) or mycelia (with long branching filaments).

Protozoa

They are unicellular parasites such as malarial parasite and amoebae.

Metazoa

They are multicellular parasites, such as tapeworm, hookworm and blood or liver flukes.

Rickettsia

These are small organisms related to bacteria structurally, but multiply intracellularly like viruses, causing diseases like typhus fever.

Reservoir of Infection

Generally, disease causing organisms do not remain viable outside the living body for a long time. They need to enter the body or tissues of humans, animals, insects or plants which serve as reservoirs of infection. Of these, the human reservoir is the most significant in a clinical situation. Organisms capable of causing disease in man are derived from human, animal or inanimate sources. The relative importance of the three sources depends primarily on the fact that different organisms are adapted to different natural habitats.

Human Sources

Individual's own organisms A normal human infant is free of microbes at birth, but rapidly acquires a complex bacterial flora

from other human beings. This flora, though harmless under ordinary circumstances, may produce diseases in favorable circumstances. *Bacteroides*, *E. coli* and other organisms are harmless commensals of the gut but can cause peritonitis if the bowel wall is mechanically damaged; *E. coli* is also the most common cause of urinary tract infection. *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Streptococcus viridans* live harmlessly in the upper respiratory tract, but can cause bronchitis, bronchopneumonia, sinusitis and otitis media, etc., if the mucous membrane is damaged by moisture, common cold or influenza. Injuries and operation wounds also offer abundant scope for endogenous bacterial infection.

Patient incubating a disease During the incubation period of an infectious disease, the prospective patient may remain apparently healthy but highly infectious. Patients of illnesses like chickenpox and hepatitis A may transmit the infection to other persons during the incubation period, shortly before they become symptomatic. In hepatitis A, the feces are infectious for about 2 weeks prior to the onset of jaundice. In hepatitis B, the blood is infectious for more than a month before the clinical symptoms set in. In rubella, mumps and poliomyelitis, the upper respiratory tract is a source of infection for a few days before the onset of symptoms. Patients who are infectious while incubating a disease are referred to as incubatory carriers.

Patient with overt disease A patient suffering from an acute or chronic infectious disease frequently throws out a large number of the causative organisms into the environment through various body fluids: feces, urine, droplets or discharges from the mouth, nose, ears, eyes and discharges of pus from internal organs, wounds, ulcers, sores and other skin lesions. In acute infections, the organisms are secreted for a short while only, while in certain chronic conditions like tuberculosis, the organism may continue to get excreted for a longer duration.

All infected individuals are not necessarily a source of infection for others—the pathogen may get lodged in a deep-seated organ, such as the meninges from which exit to another host is impossible (e.g., neurocysticercosis, toxoplasmosis). On the other hand, the pathogen may be so virulent as to kill the host and annihilate itself in the process. Patients suffering from grave life-threatening, infectious illnesses have a poor prognosis but they often do not pose significant hazard to the community—since such patients are usually confined to bed or isolated, and do not commonly come in contact with other unaffected persons in the community, except with their own family members or immediate attendants and neighbors. These patients are often diagnosed early and are treated appropriately to eliminate the reservoir of infection and make them non-infective.

Convalescent carriers In many infectious diseases, the causative organisms are not eliminated even after the clinical recovery has taken place. The organisms may persist in the throat following diphtheria or streptococcal sore throat, and may continue to be excreted in the feces after recovery in typhoid, dysentery or poliomyelitis. Such individuals are known as convalescent carriers or convalescent excretors. The carrier state is usually temporary but may persist longer in around 10% cases. Those who shed the organisms for less than a year are known as temporary carriers. Chronic carriers keep on excreting the organisms for more than a year following an illness, e.g., typhoid fever.

Contact carriers Persons in contact with a patient suffering from an infectious disease may acquire the organism and harbor it without suffering from any apparent disease; patients who have recently recovered from an infection may continue to discharge the organisms for several weeks during convalescence. Such individuals are known as contact carriers and asymptomatic excretors, respectively. Contact carrier state may be temporary

or prolonged. The interaction between the host and the parasite may result in a very mild form of the disease, or a relationship, which can best be regarded as commensalism. In an outbreak of poliomyelitis, cases of the overt disease are greatly outnumbered by cases of inapparent or subclinical infection, which are nevertheless infectious. A high proportion of healthy hospital workers carry *Staphylococcus aureus* on their skin and nose, and are undesirably the most important source of hospital-borne infection. Other diseases, where contact carriers are common, include diphtheria, streptococcal sore throat, meningococcal meningitis, dysentery and hepatitis B. Contact carriers constitute a special hazard for they have a disease that is subclinical.

Animal Sources

Infectious diseases, which are transmitted naturally between vertebrate animals and men are called *zoonoses*. These may be classified on the basis of their etiology, reservoir or the life cycle of the infecting organism (**Box 2**). Cows may excrete *M. tuberculosis* or *Brucella abortus* in their milk and *Campylobacter jejuni* in feces. The viruses of cowpox and milker's node may be present in lesions on the udder. They are often infected with ringworm fungi and sometimes with the beef tapeworm, *Taenia saginata*. Goats in the Mediterranean region may excrete brucella in their milk and may be infected with *Bacillus anthracis*. Sheep are the natural source of the liver fluke, *Fasciola hepatica*. Horses excrete *Clostridium*

BOX 2 Classification of zoonoses with respect to etiology, reservoir or life cycle of the infecting organism

With respect to etiology

Bacterial zoonoses	Brucellosis, anthrax, plague, salmonellosis.
Viral zoonoses	Rabies, Japanese encephalitis and other arboviral infections.
Parasitic zoonoses	Toxoplasmosis (protozoan), hydatid disease (helminthic), myiasis (ectoparasitic).
Fungal zoonoses	Histoplasmosis, cryptococcosis, superficial dermatophytic infections (some).
Rickettsial zoonoses	Murine typhus, tick fever, Q fever.

With respect to reservoir

Anthropozoonoses	Infections transmitted from the lower vertebrate animals to man.
Zooanthroponoses	Infection primarily of human origin, transmitted from man to lower vertebrate animals.
Amphixenoses	Infection maintained in man and lower vertebrate animals and may be transmitted in either direction.

With respect to life cycle of the infecting organism

Direct zoonoses	Infection transmitted from the infected vertebrate host (animal) to a susceptible vertebrate host (e.g., man), either by direct contact, contact with fomites or by mechanical transmission through a vector. During transmission, the agent undergoes no developmental or propagative changes (e.g., trichinosis).
Cyclozoonoses	Infection requires more than one vertebrate host species in order to complete the life cycle of the agent. No invertebrate hosts are required (e.g., echinococcosis, taeniasis).
Metazoonoses	Infection is transmitted biologically by the invertebrate vectors, e.g., mosquito. The parasite characteristically develops or multiplies in the invertebrate. There is a mandatory pre-patent period (extrinsic incubation period) before the agent can be transmitted back to a susceptible vertebrate host (e.g., kala-azar and dengue fever).
Saprozoonoses	Infection is transmitted from the inanimate developmental sites or reservoirs such as soil, plant and food to the susceptible vertebrate hosts (e.g., larva migrans).

tetani in their feces and are often infected with ringworm fungi. Dogs transmit rabies virus by their bite, leptospira in their urine, ringworm fungi by contact with their skin and hair, and the ova of the hydatid-worm *Echinococcus granulosus* and the roundworm *Toxocara canis* through their feces.

Cats can be a source of ringworm fungi. *Toxoplasma gondii* may be transmitted by the feces of the cat containing its oocyst. Monkeys are the natural hosts of yellow fever virus and also dengue fever virus in some areas. These diseases are conveyed to man by mosquitoes. Pigs may be infected with *Brucella suis*, *Salmonellae*, *Balantidium coli*, the pork tapeworm *Taenia solium* and the nematode *Trichinella spiralis*. Rats may be infected with *Yersinia pestis* and transmitted to man by fleas, resulting in plague. Leptospira may be excreted in urine and enter the human body through cuts and abrasions. Rat bite fever occurs due to *Spirillum minus* or *Streptobacillus*. Rats commonly excrete *Salmonellae* in their feces. They are the natural host of the virus of lymphocytic choriomeningitis. Chickens, turkeys and ducks can excrete *Salmonellae* in their feces. These organisms frequently contaminate the meat. Duck eggs are liable to contain *Salmonellae*. Parrots, pigeons and other birds may excrete the organisms of psittacosis (*Chlamydia psittaci*) and ornithosis in their feces. Tortoises, terrapins, turtles and lizards may excrete *Salmonellae*. Fish may be infected with *Vibrio parahaemolyticus* and the fish tapeworm, *Diphyllobothrium latum*. Various domestic and wild animals are the natural hosts of *Listeria monocytogenes*, *Yersinia enterocolitica* and *Pasteurella haemolytica*. Wild animals are also hosts for rickettsiae causing various types of typhus fever, arboviruses causing encephalitis and febrile illness and various protozoa, such as trypanosomes. These diseases are transmitted by arthropod vectors.

Inanimate Sources

Pseudomonas, *Proteus* and many species of *Clostridium* are capable of a free-living existence in the soil where they obtain nourishment from decaying animals and vegetable matter. They are also common intestinal commensals of man and animals and may be returned to the soil in their feces. These organisms show little tendency to produce disease spontaneously. *Pseudomonas* and *Proteus* may infect burns, wounds and urinary tract; *Clostridia* may produce tetanus and gas gangrene under anaerobic conditions, such as a deep wound contaminated with soil.

Transmission to Host

The infecting organisms may be transferred from the reservoir to the host either *directly* or *indirectly*. **Box 3** depicts the common routes of exit of an agent from the reservoir and entry into the host.

BOX 3 Routes of exit and entry of microorganisms

A. Routes of exit from the reservoir

1. *Respiratory tract* during processes of normal breathing, speaking, sneezing, coughing and through sputum
2. *Gastrointestinal tract* in the feces
3. *Urinary tract* in the urine
4. *Skin* through superficial lesions, such as in impetigo, chickenpox and syphilis
5. *Genital tract*, such as cytomegalovirus, rubella, toxoplasmosis, *Chlamydia*, HIV and semen as in AIDS

B. Routes of entry into a new host

1. *Inhalation*: Airborne inhalation and infection through the respiratory tract
2. *Ingestion*: Food-borne ingestion and infection through the alimentary tract
3. *Inoculation*: Inoculation through skin and mucous membranes
4. *Transplacental*: From mother to fetus.

Direct Transmission

The etiologic agent is transmitted directly into the host through: (i) either from skin to skin (impetigo and sexually transmitted diseases, such as hepatitis B, AIDS, herpes and syphilis); or (ii) by droplet spread through coughing, talking and sneezing as in measles, chickenpox, tuberculosis and even leprosy.

Transmission can occur only in a susceptible host, in an overcrowded place within 1–2 m of the patient, who is transmitting the agent. Droplets of mumps and rhinovirus that fall on the ground are not able to infect the host, but mycobacteriae of tuberculosis and leprosy are potentially viable for some time and can become a part of the household dust and thus contaminate the air.

Indirect Transmission

The etiologic agent may be transmitted to a host who may be at a distant site, through the following mechanisms:

Vectors Vectors include ticks, mites and insects, such as fleas, flies, lice and mosquitoes. They might transmit the infection mechanically by carrying the organisms on their feet or wings. Infecting agent may actually grow in the body of the vector, e.g., malarial parasites in mosquito.

Vehicles These include air, dust, water, milk, food, clothing, bedding, medical, surgical and dental instruments, appliances, dressings, books and toys contaminated by a patient and are referred to as fomites.

Modes of Transmission

Airborne Transmission

During breathing, moist surfaces of nasopharynx and lower respiratory tract trap the organisms in the contaminated air. This is the usual mechanism of transmission of streptococcal sore throat, diphtheria, meningococcal meningitis, whooping cough, pulmonary tuberculosis, plague, measles, influenza and the common cold. The organisms may reach the recipient by *direct transfer*, *droplet infection* or *through dust*.

Droplet infection A small number of organisms escape into the air from the nose or mouth during normal expiration or in quiet conversation. Coughing and sneezing and nose blowing result in the release of a vast number of organisms into the air from the mouth and the nose respectively. Particles from the respiratory tract are released in the form of droplets—a vigorous cough may liberate 5,000 and a vigorous sneeze, as many as a million droplets. Most droplet nuclei are sterile and even in patients infected with severe and contagious infections, such as with *Mycobacterium tuberculosis*, *Streptococcus pyogenes* and *Corynebacterium diphtheriae*, only a minute proportion of droplets contain the pathogen. Some of these droplets have a diameter of 100 nm or more but most of them are less than 100 nm. The smaller droplets evaporate almost instantaneously and remain suspended in the air for many hours as droplet nuclei before falling to the ground. Larger droplets have an extremely short trajectory and fall rapidly towards the ground and contaminate whatever is immediately in front and below the patient. Even in vigorous coughing or sneezing, these droplets do not travel for more than 0.5–0.75 m in a horizontal direction. Larger droplets contain more organisms but their short trajectory limits their ability to cause direct infection. A cough or sneeze aimed directly at the face of the victim is a certain way of transferring infection.

Both bacterial and viral diseases can be spread by droplet infection, particularly the latter. Droplet infection is of specific importance in the spread of bacteria such as *Neisseria meningitidis* and *Bordetella pertussis* which are rapidly killed by drying. In other diseases, the expulsion of droplets may be a more important source of contaminating the environment.

Dust-borne infection An infected person firstly contaminates himself and his environment by releasing droplets or by direct outflow of secretions. Later on, the organisms in droplets or secretions are conveyed to the recipient in the form of dust. People who carry *S. aureus* and *Streptococcus pyogenes* in their nose or throat are also likely to have them on their skin, hands, face, clothing, handkerchief, pockets and on objects with which they are in close contact, e.g., bedding, handbags, books, pens, etc. The infected secretions dry on whatever they happen to contaminate. Many organisms will survive for days or weeks even under these conditions if they are shielded from direct sunlight (e.g., *M. tuberculosis*, *Streptococcus pyogenes*, *S. aureus* and *Corynebacterium diphtheriae*). Large number of dust particles is liberated from the skin, clothing and fomites during normal body movements, and at the time of other household processes, such as bed making, sweeping and dusting. Inhalation of such infected dust particles is an important mode of infection for many bacterial diseases of the respiratory tract.

Gastrointestinal Transmission

Infection through gastrointestinal tract may be acquired by directly ingesting the organisms themselves (e.g., *Salmonellae*, *Shigellae*, *E. coli*, *Vibrio cholerae*, *Campylobacter jejuni*, *Yersinia enterocolitica*, rotavirus, cysts of the protozoa *Entamoeba histolytica* and *Giardia lamblia* and ova of various intestinal helminthes, such as roundworms and tapeworms) or their pre-formed toxins (e.g., toxins of *S. aureus* and *Vibrio cholerae*). *Clostridium perfringens* forms toxin in the gut thereby causing disease. Certain organisms enter by the intestinal tract but cause their main symptoms elsewhere (e.g., *Brucella*, hepatitis A, polio, coxsackie and echoviruses and *Toxoplasma gondii*).

The feces of a case or carrier is by far the most important source of the intestinal pathogen. Occasionally, the organisms may also be excreted in the urine, e.g., in enteric fever. Milk and water also constitute important modes of infection through ingestion.

Direct contamination Objects may be contaminated by feces or by the hands. When a patient has diarrhea, contamination is more likely by touching the patient or fomites contaminated with fecal material. Subsequently, the recipient may transfer infection to his mouth by means of fingers, eating utensils, feeding bottles and other objects. *Shigella* dysentery and *E. coli* diarrhea are frequently spread in this manner.

Food-borne infections These may be caused by a carrier engaged in handling and preparing food, or by the contaminated food itself. Affected individual may thus present either as a case of food poisoning or infective diarrhea. Milk offers an excellent medium for multiplication of certain bacteria unless it is refrigerated. Pathogens in the milk may be derived from the cows, (e.g., *M. bovis*, *Brucella abortus*, *Coxiella burnetii* and *Campylobacter jejuni*) or get introduced by dairy workers, or by contaminated water or equipment (e.g., *Streptococcus pyogenes*, *C. diphtheriae*, *Salmonellae*, and *Shigellae*). Certain other organisms turn the milk sour but are harmless, e.g., *E. coli* and lactobacilli. All the pathogens are killed by pasteurization.

Food poisoning Consumption of contaminated food at community gatherings frequently results in large outbreaks of diarrhea and vomiting. Most food poisonings are bacterial in origin—staphylococcal food poisoning is due to the consumption of preformed enterotoxins, while *Clostridium perfringens* food poisoning is caused by ingesting a large dose of the organisms which then release the toxins in the gut. Such type of poisoning is not infective by contact. The onset is usually explosive and majority of the individuals are influenced within a few hours after

consumption of the affected food (e.g., 2–6 hours with *S. aureus* and 6–12 hours with *Clostridium perfringens*). The symptoms may be severe but rarely last for more than 24 hours. Prostration is common and pyrexia does not occur. Vomiting is unusual in *Clostridium perfringens* food poisoning.

Water-borne infections These occur by seepage from a privy cesspit, or sewer into a well or water supply, or by direct pollution of water by a carrier; water may itself spread infection or contaminate food. Water-borne infections have been responsible for many major epidemics of cholera and typhoid in the past. Improvement in sewage disposal, water purification and piped supply are the basic requirements to contain water-borne infections.

Transmission through Inoculation

Through intact skin The venereal diseases, syphilis and gonorrhea are spread by contact of genital mucous membranes and very rarely by other means. Close physical contact is important in the spread of: (a) skin infections, such as impetigo, boils, warts, herpes simplex and ringworm; (b) diseases which affect the skin, such as leprosy, yaws, and the rashes of secondary syphilis; and (c) infection of the conjunctivae caused by *Chlamydia trachomatis*.

Through a break in the skin Wound infection follows a break in the continuity of skin or mucous membranes. This may happen following accidental injuries, burns, surgical procedures and childbirth. *S. aureus* is one of the most common pathogenic organisms responsible for wound infection. Patients with staphylococcal infections are likely to contaminate their immediate environment and other individuals in the community unless elaborate precautions are taken. Transfer of infection to clean wounds from other patients with septic lesions is more commonly the result of airborne contamination rather than by direct inoculation—*Clostridium perfringens* and *Clostridium tetani* are introduced at the time the wound is inflicted. The same applies to rabies virus, which is acquired from the bite of a rabid animal, usually a dog. *E. coli* and bacteroid infections may follow abdominal surgery due to lapses in hygienic precautions.

Blood-borne Hepatitis B virus is present in the blood of certain individuals and the most important mechanisms by which it is transmitted to another human being is by injection—e.g., by using needles and syringes contaminated with traces of human blood, and improperly sterilized equipment of dentists, chiropodists, acupuncturists, tattooists, barbers, ear-piercers, etc., and blood transfusion. Hepatitis C virus, HIV, human T-lymphotropic virus (HTLV) and cytomegalovirus may also get transmitted by transfusion of improperly screened blood.

Vector-borne Arthropod vectors are important in the transmission of diseases caused by arboviruses, protozoa, some helminths, rickettsiae and a few bacteria (**Box 4**). Insects become infected when they bite a host whose blood contains the particular organisms. They do not behave as passive carriers, as do flies in transmitting *Salmonellae* and *Shigellae* from feces to food, but act as a host in which the organisms can multiply. There is normally

BOX 4 Vectors and diseases

Mosquitoes	Malaria, yellow fever, dengue, Japanese encephalitis, filariasis
Sandflies	Sandfly fever, leishmaniasis
Tse-tse flies	Trypanosomiasis
Fleas	Bubonic plague, murine typhus
Lice	Epidemic typhus, trench fever
Ticks	Kyasanur forest disease, Rocky mountain spotted fever
Mites	Scrub typhus, Rickettsial pox.

an interval of several days before the insects are capable of transmitting infection (extrinsic incubation period).

Lower animals are the natural hosts of most diseases transmitted to man by biting insects. In some, however, man is the primary host and there is no animal reservoir of infection; for example, epidemic typhus, sandfly fever and malaria are transmitted by insect from man to man.

Transplantation Transplant material, such as kidneys, bone marrow and corneal grafts may convey infection from one person to another. The infecting agent is most commonly a virus that has been lying dormant in the tissues of the donor. In the recipient, the virus becomes reactivated because of the low host resistance brought about by immunosuppressive therapy. Cytomegalovirus is the most frequent offender. Corneal graft and growth hormone therapy have on occasion transmitted serious prion disease, Creutzfeldt-Jakob disease.

Transplacental Transmission

Placenta is an effective barrier to infection. Certain organisms including the bacteria (*Treponema pallidum*, *Listeria*), viruses (rubella, cytomegalovirus, hepatitis B virus) and protozoa (toxoplasma) may, however, readily cross the placenta and cause fetal afflictions. Rubella virus infection in the first trimester of pregnancy frequently produces congenital abnormalities in the fetus.

Multiple routes

Certain organisms can infect a host through several different portals. *M. tuberculosis* may enter the host by inhalation, ingestion, inoculation or transplacental transmission and cause disease. But, most of the organisms can produce infection only if they enter through a particular portal, e.g., *Salmonellae* can gain access through the intestinal tract but do not infect open wounds; *S. aureus* readily infects wounds but is unlikely to setup infection if ingested. The portal of entry may be located remotely from the part of the body, which ultimately bears the brunt of the disease; poliovirus enters the host through the pharynx and intestinal tract but the clinical effects of poliomyelitis spare the gastrointestinal tract and are largely confined to the central nervous system.

IN A NUTSHELL

1. The development or spread of an infectious disease requires an etiological agent; reservoir of the etiological agent; transmission of the agent from the reservoir to the new host.
2. Etiological agents include bacteria, viruses, fungi, protozoa, rickettsia and other unclassified organisms.
3. Man is the most important reservoir of microorganisms and macroorganisms causing infections. Other important reservoirs are animals and soil.
4. Microorganisms can exit the human body through coughing, sneezing, breathing, defecation, urine, cutaneous lesions and genital tract.
5. Microorganisms can invade a new host through inhalation, ingestion, injection or transplacentally.

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Chapter 27.2

Laboratory Diagnosis of Infection

Sankar Sengupta

The microbiology laboratory plays a crucial role in the diagnosis of infectious diseases. Many tests are available for the detection of infection. These include microscopic demonstration, culture isolation, serological evidence and molecular techniques.

COLLECTION OF SPECIMENS

Body fluids, secretions and biopsy material can all be examined to detect pathogens, antigens or products or the immune response to them. Samples from the environment, e.g., water, food or soil, may also be examined. Some samples must be collected at a particular time; for example, blood for bacterial culture should be taken as the fever begins to rise. Special precautions must be taken to ensure survival of the pathogen and exclude contaminants, e.g., cleaning the perineum before collecting a midstream specimen of urine. Anaerobic species may die if exposed to atmospheric oxygen and survive better in samples of pus, rather than in swab specimens. Many pathogens such as *Neisseria* and most anaerobic species die quickly outside the body and must be transported to the laboratory without delay. *Neisseria gonorrhoeae* is susceptible to drying, so specimens likely to contain this organism should be inoculated onto microbiological medium near to the patient.

Universal precautions and laboratory safety Specimens may contain hazardous pathogens and must be handled with care. A system of universal precautions is employed to reduce the risk of transmitting blood-borne viruses. These are personal protective measures, taken in collecting and examining specimens irrespective of their source. The idea is to handle specimens on the assumption that they may contain a transmissible pathogen, rather than relying on clinical suspicion or written clinical details, which may be faulty or absent. For example, any sputum specimen is assumed to carry the risk of tuberculosis even if this is not the test requested.

DIRECT MICROSCOPIC EXAMINATION

Antony van Leeuwenhoek first saw microscopic *animalcules*, and Alexander Ogston, a surgeon, described the characteristic microscopic morphology of staphylococci in pus and discovered their role in pyogenic sepsis. The light microscope has since been indispensable in the study of microorganisms. The diagnosis of malaria or vaginal trichomoniasis, for instance, can be made while the patient waits at the clinic. Unlike culture, organism sought need neither multiply nor even be alive. Microscopy is especially useful for detecting organisms that are difficult or dangerous to grow.

Direct microscopy of unstained preparations Direct examination of unstained wet preparations is suitable for rapid diagnosis of fecal protozoa and helminths; organisms in vaginal discharge; and urine for bacteria and pus cells. Viruses can also be detected directly by electron microscopy, using a negative-staining technique. This technique is useful for detecting viruses with distinctive morphology, such as poxviruses in scrapings from the lesions of orf and *Molluscum contagiosum*, herpesviruses in vesicle fluid, or rotavirus in diarrhea stools.

Gram stain Dried preparations of specimens that are fixed to kill the organisms can be examined using simple stains, such as Gram stain, that dye the bacteria. This technique can demonstrate the shape of the bacteria and the capability of gram-positive bacteria

to retain the methylene blue dye. The Gram stain provides a rapid answer to the clinical question, Are there any organisms present? It is most useful when sterile fluids such as cerebrospinal fluid (CSF) or pleural fluid are examined. However, the sensitivity of Gram stain is relatively low and at least 10,000 organisms per mL must be present for a diagnosis to be made. Gram stain preparations can be made for the following fluids:

- Sterile fluids (CSF, ascites, pleural fluid)
- Sputum (to exclude poor-quality specimens)
- Pus from any site
- Urethral discharge.

Gram staining alone can rarely detect the organism specifically, because the morphology of bacteria is rarely diagnostic. Other simple stains include acridine orange, lactophenol blue to demonstrate the morphology of fungi, or India ink (to detect *Cryptococcus neoformans* in the CSF).

Ziehl-Nielsen (ZN) stain Specimens are stained with carbol-fuchsin, destained with an acid-alcohol solution and then counterstained with methylene blue. The lipid-rich mycobacterial cell wall retains the pink dye and organisms are seen as pink bacilli against blue background. This technique is useful in the diagnosis of mycobacterial infections, including tuberculosis and leprosy, and parasitic infections, such as cryptosporidiosis. A variation of this technique uses the naturally fluorescent substance auramine to stain the organisms. However, it lacks the specificity of the ZN stain.

Romanowsky stains Romanowsky stains, which color cytoplasm and chromatin, are widely used to demonstrate blood cells. Stains of this type are very useful for revealing blood parasites. In malaria or filariasis, Giemsa-stained smears not only demonstrate the presence of the organisms, but also permit speciation by displaying morphological details.

Immunofluorescence Direct immunofluorescence techniques detect organisms by their binding with fluorescence-labeled antibodies. This technique is both sensitive and specific and provides a rapid presumptive diagnosis. It can be applied to a wide range of specimens and is used in the diagnosis of upper respiratory tract virus infections including influenza, parainfluenza and respiratory syncytial virus, also measles and rabies. Some organisms detectable by direct immunofluorescence include viruses: parainfluenza viruses, respiratory syncytial virus; bacteria: *Legionella*, *Treponema pallidum*; and protozoa/fungi: *Giardia intestinalis*, *Pneumocystis jiroveci* (carinii).

CULTURE METHODS

Culture can aid diagnosis in bacterial, parasitic and viral diseases. In bacteriology, culture permits amplification of the number of bacteria. Isolating them on solid media makes identification and susceptibility testing possible. Bacterial culture is made possible by the use of agar, a gelatinous substance derived from seaweed, which melts at 90°C but solidifies at 50°C. It is highly stable, is rarely affected by organisms in cultures and can be mixed with nutrients, such as blood, serum and protein digests to make solid media. Bacteriological culture on solid agar is usually performed in Petri dishes. When prolonged culture is necessary, as in the diagnosis of mycobacterial or fungal infection, it is usually performed in sealed containers to prevent desiccation and the entry of contaminating organisms. The choice of medium and the conditions of incubation depend on knowledge of the organism's requirements for optimum growth. Three types of bacteriological media are used: (1) enrichment; (2) selective; and (3) indicator.

Enrichment media Enrichment media ensure that small numbers of fragile pathogens (e.g., *Neisseria* or *Vibrio spp*) can multiply sufficiently to be detected. They are useful when seeking to identify fastidious organisms such as *Streptococcus spp*, *Haemophilus influenzae* or *Bacteroides fragilis*. Enrichment media are made by adding blood, yeast extracts, tissue infusions, meat, etc. to simple

base media. Some enrichment media include materials to neutralize toxic bacterial products that would otherwise inhibit growth. An example of this is charcoal in the enrichment medium for *Bordetella*. The media may be solid, for example, blood agar or liquid, as with Robertson's cooked-meat broth. Liquid media are especially valuable for investigating body fluids that are normally sterile.

Selective media Selective media are used to identify a pathogen existing in a mixture of organisms. Many body sites, such as the upper respiratory tract or the gut, have normal resident flora and pathogens must be isolated from this bacterial competition. Selective media contain compounds such as chemicals (e.g., selenite F), dyes (crystal violet) or mixtures of antibiotics that selectively inhibit the normal flora, enabling the pathogen to grow. Although selective agents have their maximum effect on the unwanted organisms, some inhibition of the target organism inevitably occurs. Therefore, an enrichment medium should also be inoculated so that small numbers of pathogens can be detected. The examples of selective media for bacteriological culture from sites containing a normal flora are shown in **Table 1**.

Table 1 Selective media for bacteriological culture

Medium	Selective agent	Specimen	Organism/s sought
Crystal violet blood agar	Crystal violet	Throat swab	<i>Streptococcus pyogenes</i>
Desoxycholate citrate	Desoxycholate	Feces	<i>Salmonella</i> , <i>Shigella</i>
New York City medium	Lincomycin, colistin, amphotericin, trimethoprim	Urethral or cervical	<i>Neisseria gonorrhoeae</i>
Selenite broth	Selenite F	Feces	<i>Salmonella</i>
Sabouraud's agar	High dextrose content	Many	Fungi

Indicator media Indicator media are used to identify colonies of pathogens among the mixture of organisms able to grow on the selective medium. Many indicator media are also selective. An example of a selective indicator medium is MacConkey's agar, which uses bile salts to select for bile-tolerant enteric organisms.

Automation

Before automation of blood cultures became widely available, it was necessary to subculture each bottle manually after 12, 24 and 48 hours, and later as necessary. Nowadays, bacterial growth is detected by the microbial production of carbon dioxide or changes in the electrical impedance of the medium, indicating the need for subculture. These detection systems (e.g., Bactec and Bact-Alert systems) provide continuous monitoring of blood culture bottles allowing earlier subculture, identification and testing of pathogens. Such methods have been adapted to *Mycobacteria*, reducing the time taken to detect a positive culture from a mean of 5 weeks to 2 weeks or less.

Limitations of culture The main limitation of traditional bacterial culture is the time required for incubation. Bacterial culture is time-consuming and labor-intensive. Matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry (MS) offers the possibility of accurate, rapid, inexpensive identification of bacteria, fungi and mycobacteria within a few minutes.

Typing Microorganisms

Typing is the use of further identification methods to distinguish between strains of organisms within the same species. Methods of typing are numerous, ranging from simple biochemical to complex

genetic characterization. There are a wide range of phenotypic typing methods, including biochemical activity, serology and phage typing, which are often used in combination. Many laboratories still type enteric pathogens, such as *Shigella flexneri* or *Salmonella* using sets of antisera raised in mice or guinea pigs (serological typing). Such methods are being increasingly superseded by genetic methods. Many molecular typing methods are now used in clinical and research practice, much improving our ability to follow outbreaks and to study the epidemiology of infection. These include *nucleic acid typing methods* that use the activity of endonuclease enzymes to split the genome into a characteristic range of different-sized fragments. Genomic or plasmid DNA, or ribosomal RNA, is harvested from the test organisms and digested with restriction endonucleases. The resulting fragments are then separated by electrophoresis or pulsed-field gel electrophoresis (PFGE) to produce a pattern of bands. The variation in band patterns is called restriction fragment length polymorphism (RFLP). This approach has proved to be especially valuable in typing *Mycobacterium tuberculosis*. Polymerase chain reaction (PCR) methods can also be used to generate DNA, from a variable gene or genes, for RFLP typing. Multilocus sequence typing is a newer type of PCR-based typing method.

Culture of Protozoa, Helminths, Viruses

Culture of protozoa and helminths tends to be difficult and often produces no better diagnostic yield than microscopy. Viruses and chlamydiae are obligatory intracellular pathogens. So culture for these organisms must be performed in living cells or tissues. Viral growth in cell culture is further detected by virtue of one or more of the following properties: cytopathic effect, hemagglutination, antigen detection, or use of electron microscopy.

SEROLOGY

Serological techniques depend on the interaction between antigen and specific antibody. They are of particular value when the pathogen is difficult or impossible to culture, or is dangerous to handle in hospital laboratories. The process can be divided into two parts, first, the antigen-antibody interaction; and next, the demonstration of this interaction by a testing process. The sensitivity of a serological test depends partly on the specificity and strength of the antigen-antibody reaction, but mostly on the ability of the test system to detect the reaction. In older tests, antibody-antigen binding was detected by observing a natural consequence of this interaction: precipitation, agglutination or the ability of the antigen-antibody complex to bind and activate (fix) complement. Some laboratory tests based on these reactions are still in daily use. Newer tests use *labeled* immunoglobulin molecules to facilitate detection. The main methods employed are labeling with fluorescein or enzymes.

Agglutination Tests

Agglutination tests are used to identify the species or serotype of an infecting organism, by observing the aggregation of a suspension of bacteria in the presence of specific antibody. They can be performed on glass slides termed as *slide test* and are used for fecal pathogens such, as *Salmonella*, *Shigella* or respiratory pathogens e.g. *Streptococcus pneumoniae*. Agglutination is also used in biomarkers detection in fungal infections by *Candida* and *Aspergillus*. *Tube agglutination* is widely used in *Brucella* standard agglutination tests and Widal test for typhoid.

Coagglutination Specific antibodies can be attached to uniform latex particles, or killed protein A-possessing staphylococci. These particles will be agglutinated when they attach in large numbers to antigen molecules. In this way, otherwise soluble immune complexes may be detected in an agglutination reaction. Such latex and coagglutination techniques are used to detect the presence of the polysaccharide antigens of *S. pneumoniae*, *H. influenzae* type b, *Neisseria meningitidis* and *C. neoformans* in CSF, or *Streptococcus pyogenes* in throat swabs.

Indirect Fluorescent Antibody Tests

Specific antigen is fixed onto a multiwell microscope slide and patient's serum added. The slide is incubated, and then washed. Fluorescein-labeled antihuman immunoglobulin is then added, followed by further incubation. After a final wash, the slides are examined under ultraviolet illumination. Where antibodies from the patient's serum have bound to the antigen, the antihuman globulin will bind, and is indicated by apple-green fluorescence. Individual positive sera may be titrated. Indirect immunofluorescence is both sensitive and specific, but rather time consuming. It is used in the diagnosis of a number of infections, especially where the throughput of specimens is small, for instance in the diagnosis of syphilis [fluorescent treponemal antibody (FTA test)] or parasitic disease, such as leishmaniasis or amebiasis.

Enzyme-linked Immunosorbent Assay

Either the antigen or antibody in the reaction is allowed to bind to a solid phase, such as the walls of microtiter wells. Four variations of enzyme-linked immunosorbent assay (ELISA) are described:

Antibody-detecting ELISA tests In an antibody-detecting ELISA, specific antigen is coated onto the wells of a microtiter ELISA plate. The patient's serum is added and any specific antibody binds to the antigen (antibody-capture). The plates are then washed and enzyme labeled antihuman immunoglobulin is added. Plates are washed again and substrate for the enzyme is added. The enzyme-substrate reaction generates a color, which indicates the specific antibody interaction. The optical density of the wells is measured by an ELISA reader. A positive result can be determined by reference to control values. It is difficult to use an antibody capture assay to answer any question other than: Is there antibody present? If a diagnosis is to be made on a single specimen, specific immunoglobulin M (IgM) must be detected. This can be achieved by purifying an IgM fraction from the serum and retesting this in an antibody detection test. A simpler alternative is the IgM antibody-capture ELISA described below.

IgM antibody-capture ELISA By placing antihuman IgM antibody on the solid phase, it is possible to capture all IgM antibodies. After washing, labeled antigen is placed in the well so that if the serum contains antigen-specific IgM, the labeled antigen will bind. A positive result is detected by adding substrate, when a color will be produced by the enzyme-labeled antigen.

Antigen-capture ELISA Antibody to a specific antigen is bound on the solid phase. If antigen is present in the specimen, it will bind to the antibody. After washing, the bound antigen is then detected by enzyme-labeled specific antibody. The amount of antigen present can be quantified by reference to an antigen standard curve.

Competitive ELISA Competitive ELISA is a technique that is particularly useful for the measurement of antigen concentrations and is also used to detect antibodies or antibiotic concentrations.

Western Blotting (Immunoblotting)

Microbial proteins can be separated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) and transferred electrophoretically to a nitrocellulose membrane. Strips of the membrane are exposed to the patient's diluted serum so that any antibodies specific to microbial proteins are bound, and can be detected using enzyme-labeled antihuman antibodies. The pattern of antibody recognition can be used to confirm a diagnosis and to demonstrate the stage of disease by the repertoire of antibody specificities that the patient has developed. This is useful in the diagnosis of Lyme disease, in which simpler serological techniques are unreliable. It is also used in the study of human immunodeficiency virus (HIV) seroconversion illnesses.

MOLECULAR AMPLIFICATION METHODS

Polymerase Chain Reaction

In a PCR, a reaction mixture consists of the specimen together with a pair of primers (short sequences of nucleotides specific for a nucleic acid sequence of the pathogen sought). Nucleotides and Taq polymerase (an enzyme that catalyzes the construction of DNA but is stable at high temperatures) are added. The reaction mixture is heated to separate all DNA strands. The primers bind to their target sequences, if they exist in the specimen, and are then annealed by cooling the mixture. The Taq polymerase adds nucleotides to make double-stranded DNA fragments. At the end of one cycle, there are, therefore, two copies of the nucleic acid sequences bound by the primers. The cycle of temperature manipulations is repeated, allowing exponential multiplication of these sequences. In positive reactions, the amplified sequences are detected by a variety of methods including the characteristic size of the product, or by hybridization.

A range of different nucleic acid amplification tests (NAATs) have followed the development of PCR. These use different reaction procedures, which all result in amplifying the target nucleic acid DNA. NAAT methods can be modified to demonstrate viral RNA by using reverse transcriptase to make DNA, which is then amplified in the usual way. It has been applied to the diagnosis of many viral diseases, including HIV, cytomegalovirus and some, such as hepatitis C, whose agent cannot be cultivated. NAAT methods have transformed viral diagnosis, allowing rapid detection of many pathogens. It is also transforming other disciplines in microbiology. A most important development has been the introduction of *real time* NAAT. For many pathogens, NAATs are significantly more sensitive than conventional culture methods, improving the diagnostic rate. An example of this is *Chlamydia*.

Applications of Molecular Amplification Methods

Detection of pathogens that grow slowly or that cannot be cultured A major advantage of NAAT is that it avoids the need to await growth of the organism in culture. This is especially important for virology where tissue culture is complex, expensive and slow and many common viruses cannot readily be cultured. Tuberculosis can be reliably diagnosed by NAAT in one day, compared to the many weeks required for culture. NAAT methods obviate the need for culture of dangerous organisms in the diagnosis of Lassa fever or anthrax. They have also been adapted for detection of bioterrorist attacks by allowing workers to detect suspected organisms in minutes using handheld devices.

Use of NAAT in routine bacteriology One of the disadvantages of NAAT is that it only detects the organisms that match the chosen test. In clinical practice, one of a range of organisms may be causing the patient's illness, and it would be impractical to apply numerous specific NAATs to search for them all.

Susceptibility testing The molecular basis of drug resistance is now becoming clear. For some organisms, the presence of a particular gene is associated with resistance to antimicrobial agents, for example, the *Pfmdr* gene in multidrug-resistant *Plasmodium falciparum*. HIV readily mutates to resistance, and the nucleotide sequence of the affected genes (protease and reverse transcriptase genes) can confirm the resistance and indicate which other drugs may also be affected. High-density DNA arrays can identify patterns of relevant genes in a microorganism, in a single procedure.

Response to treatment Amplification techniques can be useful in showing the early response to treatment. Examples include their use in measuring the response to antituberculosis therapy; the number of organisms in a respiratory sample can be estimated, using limiting-dilution PCR. A quicker alternative is to detect bacterial mRNA, which implies the presence of viable organisms allowing the success or failure of therapy to be judged. In managing HIV and hepatitis C infections, PCR is used to quantify the number

of viral genome copies in the serum (viral load). The progress of treatment can be followed by serial measurements.

IN A NUTSHELL

1. An important skill in clinical infectious diseases and microbiology is the choosing of appropriate diagnostic investigations.
2. Timely and accurate diagnosis depends on obtaining the correct specimen at the optimum time of collection. Specimens must be transported to the laboratory quickly and in conditions that maintain the viability of the organisms present or the integrity of the antigen or DNA sought.
3. Molecular diagnostic techniques now provide microbiologists with the possibility of providing a diagnosis more rapidly than was possible with culture-based methods.
4. In the laboratory, the correct diagnostic method must be used and the results effectively communicated to the doctor managing the case. This process depends on close cooperation between clinician, microbiologist and laboratory scientists.

MORE ON THIS TOPIC

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Chapter 27.3

Antimicrobial Resistance

Anuradha De

Antimicrobial resistance (AMR) is a global problem in the hospitals as well as in the community and is listed at the top of the Centers for Disease Control and Prevention (CDC) list of emerging infectious threats to the public health. *Relentless and dizzying rise of antibiotic resistance* has contributed to the persistence of infections as a major cause of morbidity and mortality and have resulted in a number of microorganisms becoming resistant or multidrug resistant (MDR) to different antimicrobial drugs.

DEFINITION

Antimicrobial resistance is resistance of a microorganism to an antimicrobial drug, to which it was originally sensitive. Resistant organisms are able to withstand attack by antimicrobials (antibiotics) so that standard treatments become ineffective and infections persist, increasing risk of spread to others. The evolution of resistant strains is a natural phenomenon that happens when microorganisms are exposed to antimicrobial drugs and resistant traits can be exchanged between certain types of bacteria. The mechanisms of drug resistance are complex and microbes often outsmart humans. Hospitals are considered the epicenters of drug-resistant microorganisms.

EMERGING THREAT

The seriousness of AMR is reflected by a steadily increasing frequency of resistance over time among individual pathogens, increased presence of resistance among critical bacterial species causing common infections, and global extent of the resistance problem. The major cause of AMR is overuse and misuse of antimicrobial agents. Studies indicate that antibiotic use is unnecessary or inappropriate in as many as 50% of cases and this creates unnecessary pressure for the selection of resistant species. Also, there is an increased pressure to prescribe antimicrobial agents as a result of invasive medical technology and indwelling devices. Government policies also do not restrict direct over-the-counter purchase of antimicrobial agents by consumers, resulting in misuse. **Box 1** summarizes the reasons for AMR being a cause of global concern. Major concerns are listed in **Box 2**. **Figure 1** presents a timeline over which several antibiotics have developed resistance.

NATURAL VERSUS ACQUIRED RESISTANCE

Intrinsic or natural resistance Microorganisms naturally do not possess target sites for the drugs and, therefore, the drug does not affect them, or they naturally have low permeability to those agents because of the differences in the chemical nature of the drug and the microbial membrane structures, e.g., *Mycobacterium tuberculosis* is insensitive to tetracyclines. This type of resistance does not pose significant clinical problem.

Acquired resistance When a naturally susceptible microorganism acquires ways of not being affected by the drug to which it was earlier susceptible, the resistance is acquired. Resistance can be acquired by several methods:

Mutations in chromosomal genes or by the acquisition of mobile genetic elements, such as plasmids or transposons, which carry the antibiotic resistance genes. It may be due to sequential accumulation of chromosomal mutations in different drug-resistant genes, as in the case of multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant TB (XDR-TB).

BOX 1 Why antimicrobial resistance is a global concern

- Infections caused by resistant microorganisms often fail to respond to the standard treatment, resulting in prolonged illness and greater risk of death
- Antimicrobial resistance reduces the effectiveness of treatment; patients remain infectious for a longer time, increasing the risk of spreading resistant microorganisms to others
- Antimicrobial resistance increases the costs of health-care by use of more expensive therapy, longer duration of treatment and increased cost of diagnostics
- Antimicrobial resistance threatens health security and damages global trade.

BOX 2 Major concerns in antimicrobial drug resistance

- Methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-resistant *Staphylococcus epidermidis* (MRSE)
- Vancomycin intermediate-resistant *Staphylococcus aureus* (VISA) and vancomycin-resistant *Staphylococcus aureus* (VRSA)
- Methicillin-resistant coagulase-negative *Staphylococcus aureus* (MRCoNS).
- Inducible clindamycin resistance (ICR) in staphylococci and streptococci
- Vancomycin-resistant enterococci (VRE)
- Penicillinase-producing *Neisseria gonorrhoeae* (PPNG)
- The ESKAPE bugs—*Enterococcus*, *Staphylococcus*, *Klebsiella*, *Acinetobacter*, *Pseudomonas*, *Escherichia coli*/Enterobacter. These are responsible for two-thirds of all health-care-associated infections (HAIs)
- Multidrug-resistant gram-negative bacilli (MDR-GNB) producing extended spectrum beta (β)-lactamases (ESBLs); AmpC β -lactamases, Metallo- β -lactamases (MBLs), Carbapenemase-producing bacteria and *Klebsiella pneumoniae* carbapenemase (KPC)
- Multidrug-resistant tuberculosis (MDR-TB); and extensively drug-resistant TB (XDR-TB).

Genetic resistance, which is the transfer of genetic material from one bacterium to another and can occur by transformation/transduction/conjugation. For example, in 1959, the Japanese found *Shigella* species that were resistant to sulfonamides, streptomycin, chloramphenicol and tetracycline. The resistance was due to plasmid, which carried different antibiotic resistance genes. Streptomycin-resistance genes, *strA* and *strB*, can also be carried on plasmid.

Phenotypic resistance is due to changes in the bacterial physiological state, such as the stationary phase, antibiotic persists and the dormant state.

MECHANISMS OF ANTIBIOTIC RESISTANCE

Table 1 shows the mechanisms of drug resistance in different antibiotics. **Figures 2A and B** show the various mechanisms of antibiotic resistance. Other mechanisms are as follows:

- Alteration or overexpression of the drug target in cell wall—penicillin-binding protein (PBP) for methicillin-resistant *Staphylococcus aureus* (MRSA) and change of D-Ala-D-Ala to D-Ala-D-lactate target for vancomycin-resistant enterococci (VRE)
- Enzymatic inactivation—lincosamide and streptogramin inactivating enzymes
- Loss of enzymes involved in drug activation—catalase-peroxidase (KatG) is an enzyme involved in the activation of isoniazid (INH), which produces a range of reactive metabolites including reactive oxygen species and then reactive organic radicals, which then inhibit multiple targets, including mycolic acid synthesis.

Antibiotic deployment

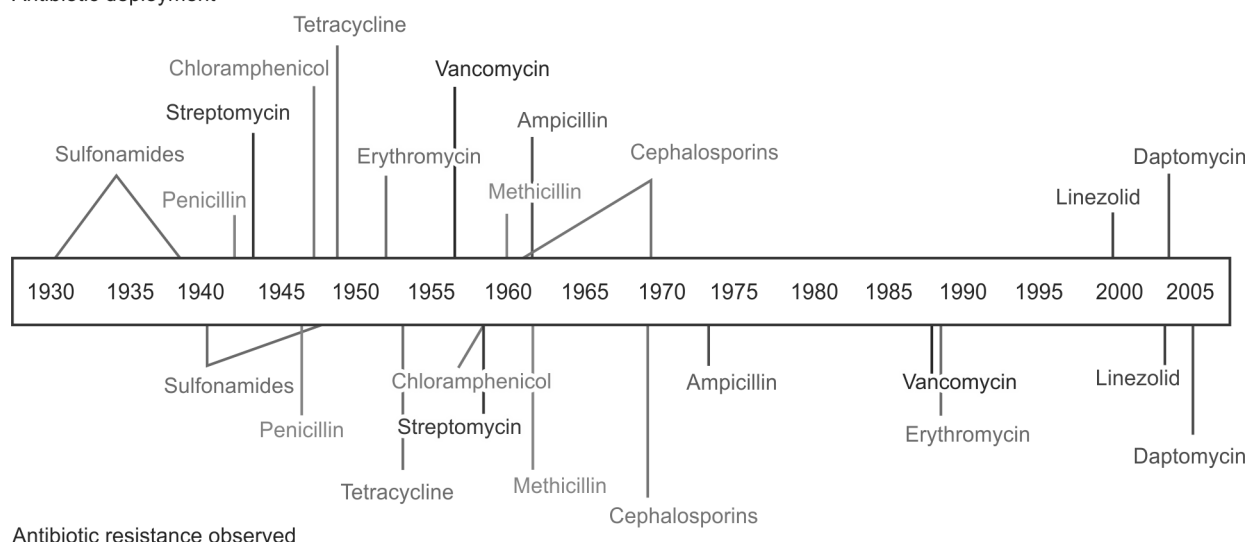


Figure 1 Timeline of antibiotic resistance

Table 1 Mechanisms of drug resistance with different antibiotics

Antibiotic	Mechanism of drug resistance
Beta-lactams	<ul style="list-style-type: none"> Enzymatic inactivation by β-lactamases Altered penicillin-binding protein Reduced permeability or uptake by loss of porins leading to increased resistance Altered gram-negative outer membrane protein Active efflux
Macrolides	<ul style="list-style-type: none"> Alteration of target (ribosomal alterations) Active efflux by <i>mef</i> gene (macrolide efflux) Enzymatic inactivation
Chloramphenicol	<ul style="list-style-type: none"> Enzymatic inactivation by chloramphenicol acetyltransferase Active efflux
Tetracycline	<ul style="list-style-type: none"> Active efflux Insensitivity of 30S ribosomal subunit Enzymatic inactivation Ribosomal alterations
Aminoglycoside	<ul style="list-style-type: none"> Enzymatic inactivation by aminoglycoside modifying enzymes Decreased permeability through gram-negative outer membrane Active efflux Ribosomal alterations
Sulfonamides and trimethoprim	<ul style="list-style-type: none"> Production of insensitive targets (dihydropterois synthetase and dihydrofolate reductase)
Quinolones	<ul style="list-style-type: none"> Mutations in DNA gyrase A and B subunits Decreased intracellular drug accumulation (active efflux)
Rifampicin	<ul style="list-style-type: none"> Mutations in <i>rpoB</i> gene encoding β-subunit of RNA polymerase
Polymyxins	<ul style="list-style-type: none"> Not defined

Beta-lactamases

Beta-lactamases are hydrolytic enzymes which cleave the β -lactam ring and are the primary mechanism of conferring bacterial resistance to β -lactam antibiotics such as penicillins and cephalosporins.

Extended spectrum β -lactamase (ESBL) was first observed in 1983 in *Klebsiella pneumoniae*. ESBLs are class A β -lactamases and may be defined as plasmid-mediated enzymes that hydrolyze oxyimino-cephalosporins and monobactams but not cephamycins or carbapenems. They hydrolyze penicillins, cephalosporins and monobactams, and are inhibited in vitro by clavulanic acid. They have the capacity to acquire resistance to other antimicrobial classes, such as the quinolones (ciprofloxacin), tetracyclines, trimethoprim-sulfamethoxazole and aminoglycosides (gentamicin and tobramycin), which further limits therapeutic options. ESBLs are primarily produced by the Enterobacteriaceae family and also by nonfermentative gram-negative bacteria.

The first plasmid-mediated metallo- β -lactamase (MBL) was reported in *Pseudomonas aeruginosa* from Japan in 1991. MBLs are metalloenzymes of Ambler class B and are clavulanic acid-resistant enzymes. They require divalent cations of zinc as cofactors for enzymatic activity and are universally inhibited by ethylenediaminetetra-acetic acid (EDTA). MBLs are commonly found in *P. aeruginosa* and *Acinetobacter baumannii*.

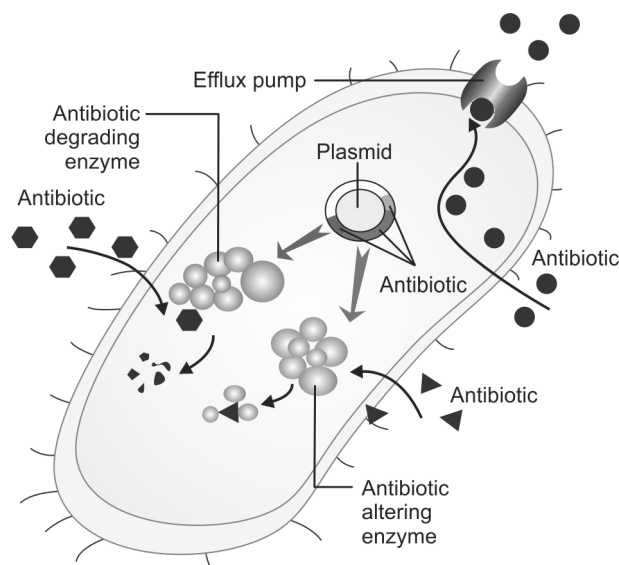


Figure 2A Mechanisms of antibiotic resistance

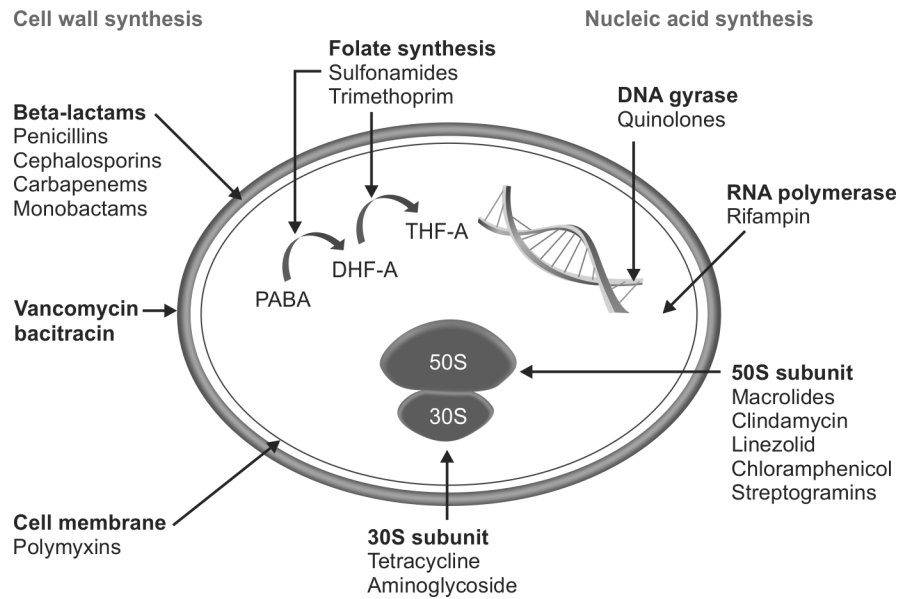


Figure 2B Mechanisms of antibiotic resistance

Klebsiella pneumoniae Carbapenemase

It was first described in North Carolina in 1999 and first isolate was reported in 2009 in sputum. *Klebsiella pneumoniae* carbapenemase (KPC) confers resistance to all β -lactams including extended spectrum cephalosporins and carbapenems. It occurs most commonly in *K. pneumoniae* or *Escherichia coli* and also reported in *K. oxytoca*, *Citrobacter freundii*, *Enterobacter* spp., *Salmonella* species and *Serratia* species. In KPC β -lactamases ~1–3% *K. pneumoniae* are resistant to carbapenems as well as to other β -lactams. They might appear susceptible to imipenem or meropenem, but with borderline MICs are usually ertapenem-resistant and susceptible only to colistin, tigecycline and select aminoglycosides.

ESKAPE Bugs

Vancomycin-resistant enterococci VRE emerged in late 1980s in France and England and subsequently has been isolated all over the world. Prolonged hospitalization, severe underlying diseases and/or immunosuppression, stay in intensive care areas, indwelling urinary or central venous catheters, etc. are the risk factors for the development of VRE.

Methicillin-resistant Staphylococcus aureus MRSA appeared in the early 1960s, soon after introduction of penicillinase-tolerant penicillins. Clones diversified and nosocomial pathogens spread into the community. Methicillin resistance now exceeds 50% in most tertiary care centers and is mainly accountable for Hospital-acquired MRSA (HA-MRSA), causing great morbidity and mortality, and thereby economic losses. This, coupled with the emergence of Community-acquired MRSA (CA-MRSA) in the recent years, poses serious clinical problems with global ramifications.

K. pneumoniae and *E. coli* ESBLs (~8–10%); 90% sensitive to carbapenems and tigecycline.

Acinetobacter traditionally infects patients in intensive care unit (ICU) and burn units. Drug resistance is a major problem in *Acinetobacter* infections, which are responsible for about 3% of all health-care-associated infections (HAIs). They are usually susceptible only to colistin.

Pseudomonas infections are usually seen in patients who are immunocompromised, debilitated, prior hospitalization, prior antibiotic therapy, trauma, etc. A particular problem is those patients on respirators and those with cystic fibrosis. One quarter of these is resistant to carbapenems.

Enterobacters also have developed broad-spectrum resistance to multiple classes of antibiotics. Tigecycline might work against these infections.

Multidrug-resistant Gram-negative Bacilli

In the recent years, the multidrug-resistant gram-negative bacilli (MDR-GNB) producing ESBLs, AmpCs and MBLs are also responsible for community-acquired infections, like skin and soft tissue infections, respiratory tract infections, urinary tract infections, etc. The major risk factors are prolonged stay in ICU, indwelling invasive devices and prior use of cephalosporins and other broad-spectrum β -lactam antibiotics. MDR-GNB cause great morbidity, mortality and economic losses. They can be effectively treated if identified properly and treatment initiated promptly, thus bringing down infection rates and preventing spread of MDR-GNB. Active surveillance of MDR-GNB in the community will help us in formulating an effective antibiotic policy based on the susceptibility pattern of MDR bacteria, which should be reviewed from time to time.

Table 2 shows the treatment and prevention of MRSA, VRE and MDR-GNB.

SURVEILLANCE OF ANTIMICROBIAL RESISTANCE

Surveillance involves the systematic collection and analysis of health-related data and dissemination to those who will use them in decision-making on public health issues. Ongoing and routine AMR surveillance enables analysis to be made of resistance rates to antimicrobials among bacteria infecting or colonizing individuals in given locations during defined time periods. Local surveillance units could be linked at national and international levels to provide national, regional and global surveillance information, insights and tools needed to guide policy on the appropriate use of antimicrobials and to inform and evaluate resistance containment interventions at local, national and global levels.

Table 2 Treatment and prevention of MRSA, VRE and MDR-GNB

	MRSA	VRE	MDR-GNB
Treatment	<p>Linezolid—protein synthesis inhibitor, used for nosocomial pneumonia and complicated skin infections</p> <p>Daptomycin—causes membrane depolarization in bacteria, so no membrane transport. It is used for bacteremia</p> <p>Clindamycin is not reliably bactericidal; D-test must be done; ~50% sensitive</p> <p>Vancomycin—acts by interfering with the construction of cell wall</p> <p>Combination of vancomycin, rifampin and cotrimoxazole</p> <p>Combination of fusidic acid and rifampin</p> <p>Third-line agents—trimethoprim-sulfamethoxazole (TMP-SMX)</p> <p>Tigecycline—works on efflux pumps</p> <p>Treatment for VISA infections are quinupristin/dalfopristin or rifampin or linezolid</p>	<p>Common sense, basic hygiene and disinfection practices can control the spread of MRSA</p> <p>Treatment options for vancomycin-resistant <i>E. faecium</i> are the newer antibiotics linezolid, daptomycin and tigecycline, but these drugs have not been studied extensively for use against these infections</p>	<p>Treating gram-negative bacterial infections can be difficult because of several unique features of these bacteria, e.g., the unique nature of their cell wall makes them resistant to several classes of antibiotics. Infections have typically been treated with broad-spectrum antibiotics, such as beta-lactams, followed by carbapenems. However, even these drugs have become ineffective against some bacteria, leaving health-care providers no choice but to use drugs like polymyxin B and colistin, which can have toxic side effects. Colistin is the last resort antibiotic for MDR <i>Pseudomonas aeruginosa</i>, MDR <i>Klebsiella pneumoniae</i>, MDR <i>Acinetobacter</i> species and MDR Enterobacteriaceae. <i>Proteus</i> species is inherently resistant to colistin</p>
Prevention	<p><i>Practising good hygiene:</i></p> <p>Enforcing hand hygiene by washing thoroughly with soap and water</p> <p>Use of alcohol-based hand sanitizers before eating and after using the restroom</p> <p>Use of gloves and not to touch unprotected body fluids</p> <p>Showering daily and after athletic practice or competition</p> <p>Keeping cuts and scrapes clean and covered with an antiseptic cream and a band-aid until healed</p> <p>Discarding used bandages and tape in garbage</p> <p>Avoiding contact with other people's wounds or bandages</p> <p>Using disposable items when treating MRSA patients</p> <p><i>Cleaning the environment:</i></p> <p>Cleaning surfaces first with wet mops and damp cloths, then disinfect</p> <p>Bleach + water 1:100/lysol/quaternary ammonium compounds</p> <p>Leaving surfaces wet for 10 minutes (if possible) or dry with paper towels</p>	<p>Proper hand hygiene, i.e., thorough washing with soap and water and then drying is the best way to prevent the spread of enterococci</p> <p>Use of alcohol-based hand rub or a household disinfectant or a mixture of one-fourth cup bleach and one quart of water to clean areas and surfaces that are touched frequently</p> <p>Wearing gloves when coming in contact with body fluids that may contain VRE</p> <p>Always washing hands after removing gloves</p> <p>The CDC Hospital Infection Control Program encourages hospitals to develop their own institution-specific plans, which should stress:</p> <p>Prudent vancomycin use by clinicians</p> <p>Hospital staff education regarding vancomycin resistance</p> <p>Early detection and prompt reporting of vancomycin resistance in enterococci and other gram-positive microorganisms by the hospital microbiology laboratory</p> <p>Immediate implementation of appropriate infection control measures to prevent person-to-person VRE transmission</p>	<p>Simple measures, such as hand-washing and health-care workers using barrier precautions can significantly reduce the spread of these bacteria</p> <p>A strict antibiotic policy should be followed in every hospital to prevent further spread of these MDR-GNB</p> <p>As these are multidrug resistant, they might pose a therapeutic challenge to clinicians as well as microbiologists</p> <p>Timely implementation of proper infection control practices reduce, eliminate and prevent establishment of MDR-GNB and prevent cross-contamination</p>

Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant enterococci; MDR-GNB, multidrug-resistant gram-negative bacilli; VISA, vancomycin intermediate-resistant *Staphylococcus aureus*.

Strategic and Technical Advisory Group on Antimicrobial Resistance

The Strategic and Technical Advisory Group (STAG) on AMR in its first report in September 2013 specifically recommended that the World Health Organization (WHO) should lead in developing a global action plan to address AMR. **Table 3** shows the WHO Global Strategy for containment of AMR. **Figure 3** shows the steps to contain AMR. **Table 4** shows the core actions. Failure to implement simple infection control practices, such as hand-washing and changing of gloves before and after contact with each patient are common causes of infection spread in hospitals.

ANTIMICROBIAL STEWARDSHIP

Antimicrobial stewardship is a key component of a multifaceted approach in preventing emergence of AMR. Good antimicrobial stewardship involves selecting an appropriate drug and optimizing its dose and duration to cure an infection while minimizing toxicity and conditions for selection of resistant bacterial strains (giving maximum benefit and minimum of adverse events). A premium has been set on maintaining the effectiveness of currently available agents.

Several strategies, including prescriber education, formulary restriction, prior approval, streamlining and antibiotic cycling

Table 3 WHO Global Strategy for containment of antimicrobial resistance

S. No.	Strategy	Recommendations
1.	Education to patients and the general community	Educate patients and the general community on the appropriate use of antimicrobials, on the importance of measures to prevent infection, such as immunization, vector control, use of bednets, etc. on simple measures that may reduce transmission of infection in the household and community, e.g., hand-washing, food hygiene, etc. and discourage patients for self-initiation of treatment
2.	Education to prescribers and dispensers	Educate all groups of prescribers and dispensers (including drug sellers) on the importance of appropriate antimicrobial use and containment of antimicrobial resistance and infection control issues; promote targeted educational programs on the accurate diagnosis and management of common infections for all health-care workers, veterinarians, prescribers and dispensers
3.	Management, guidelines and formularies	Improve antimicrobial use by supervision and support of diagnostic and treatment strategies; audit prescribing and dispensing practices and utilize peer group or external standard comparisons to provide feedback of appropriate antimicrobial prescribing; encourage development and use of guidelines and treatment algorithms to foster appropriate use of antimicrobials
4.	Hospital management	Establish infection control programs based on current best practice for effective management of antimicrobial resistance in hospitals and ensure that all hospitals have access to such a program; establish effective hospital therapeutics committees for overseeing antimicrobial use in hospitals; develop and regularly update guidelines for antimicrobial treatment and prophylaxis; monitor antimicrobial usage, including the quantity and patterns of use and feedback results to prescribers
5.	Diagnostic laboratories	Ensure access to microbiology laboratory services that match the level of the hospital, e.g., secondary, tertiary; ensure performance and quality assurance of appropriate diagnostic tests, microbial identification, antimicrobial susceptibility tests of key pathogens; timely and relevant reporting of results; ensure that laboratory data are recorded, preferably on a database and are used to produce clinically and epidemiologically useful surveillance reports of resistance patterns among common pathogens, with feedback to prescribers and to the infection control committee
6.	Interactions with the pharmaceutical industry	Control and monitor pharmaceutical company promotional activities within the hospital environment and ensure that such activities have educational benefit
7.	Use of antimicrobials in food-producing animals	Require obligatory prescriptions for all antimicrobials used for disease control in food animals; in the absence of a public health safety evaluation, terminate or rapidly phase out the use of antimicrobials for growth promotion if they are also used for treatment of humans; create national systems to monitor antimicrobial usage in food animals; develop guidelines for veterinarians to reduce overuse and misuse of antimicrobials in food animals
<i>National governments and health systems</i>		
8.	Advocacy and intersectoral action	Making the containment of antimicrobial resistance a national priority; creating a national intersectoral task-force to raise awareness about antimicrobial resistance, preferably a government task-force which receives input from multiple sectors; allocating resources to promote the implementation of interventions to contain resistance, which should include the appropriate utilization of antimicrobial drugs, the control and prevention of infection and research activities; developing indicators to monitor and evaluate the impact of the antimicrobial resistance containment strategy
9.	Regulations	Establishing an effective registration scheme for dispensing outlets; limiting the availability of antimicrobials to prescription-only status and linking it to regulations regarding the sale, supply, dispensing and allowable promotional activities of antimicrobial agents; ensuring that only antimicrobials meeting international standards of quality, safety and efficacy are granted marketing authorization; introducing legal requirements for manufacturers to collect and report data on antimicrobial distribution (including import/export); creating economic incentives for appropriate use of antimicrobials
10.	Policies and guidelines	Establishing and maintaining updated national standard treatment guidelines (STGs) and encouraging their implementation; establishing an Essential Drugs List (EDL) consistent with national STGs and ensuring the accessibility and quality of these drugs; enhancing immunization coverage and other disease preventive measures, thereby reducing the need for antimicrobials
11.	Education	Maximizing and maintaining the effectiveness of the EDL and STGs by conducting appropriate undergraduate and postgraduate education programs of health-care professionals on the importance of appropriate antimicrobial use and containment of antimicrobial resistance; ensuring that prescribers have access to approved prescribing literature on individual drugs
12.	Surveillance of resistance, antimicrobial usage and disease burden	Developing reference microbiology laboratory facilities to coordinate effective surveillance of antimicrobial resistance among common pathogens in the community, hospitals and other health-care facilities; adapting and applying WHO model systems for antimicrobial resistance surveillance and ensuring data flow to the national intersectoral task-force, to authorities responsible for the national STGs and to prescribers; establishing systems for monitoring antimicrobial use in hospitals and the community, and linking these findings to resistance and disease surveillance data; establishing surveillance for key infectious diseases and syndromes according to country priorities, and linking this information to other surveillance data
13.	Drug and vaccine development	Encouraging drug development programs; providing incentives for industry to invest in the research and development of new antimicrobials; seeking innovative partnerships with the pharmaceutical industry to improve access to newer essential drugs
14.	Pharmaceutical promotion	Introducing requirements for pharmaceutical companies to comply with national or international codes of practice on promotional activities; ensuring that national or international codes of practice cover direct-to-consumer advertising, including advertising in the Internet

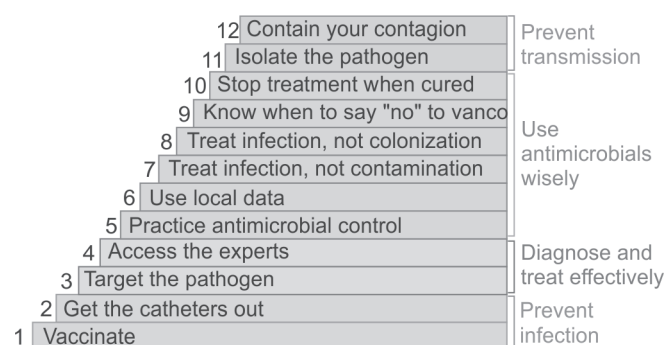
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S. No.	Strategy	Recommendations
15.	International aspects of containing antimicrobial resistance	Encouraging collaboration between governments, nongovernmental organizations, professional societies and international agencies to recognize the importance of antimicrobial resistance and its containment and to implement strategies to contain resistance; encouraging all the above to support the establishment of networks, with trained staff and adequate infrastructures, who can undertake proper surveillance of antimicrobial resistance and antimicrobial use; supporting an international approach to the control of counterfeit antimicrobials in line with the WHO guidelines; encouraging innovative approaches to incentives for the development of new pharmaceutical products and vaccines for neglected diseases; establishing new and reinforcing existing programs for researchers to improve the design, preparation and conduct of research to contain antimicrobial resistance

Table 4 Core actions to counter antimicrobial resistance at global level

• Establish AMR surveillance and monitoring systems on a regular basis, which will help to formulate standard treatment guidelines
• Build laboratory capacity for rapid and reliable diagnostic testing by designating reference microbiology laboratories to establish quality assurance systems
• Improvement of existing treatment modalities by treating infections by nonantibiotic methods, e.g., natural peptides, vaccines, monoclonal antibodies; or use of combination regimens; or by identifying new antimicrobial drug targets; or to follow the principle of rotation of antibiotics to minimize antimicrobial resistance
• Development of new treatment modalities, e.g., phage therapy
• Mobilization of host defense mechanism through the development of vaccines
• The use of normal bacterial flora to suppress some pathogens
• Adhering to the list of <i>Critically Important Antibiotics</i> for human use only
• Treat infections not colonization, e.g., treat pneumonia, not the tracheal aspirate/endotracheal secretion; treat urinary tract infection, not the indwelling catheter; treat bacteremia, not the catheter tip or hub, etc.
• Initiation of studies to understand the causes of Fever of Unknown Origin (FUO)
• Introduction of IT-enabled softwares
• Community-based studies on the prevalence and susceptibility patterns of the circulating microbes (ESBLs, MRSA, MBLs, etc.) in population
• Engage in regional and global surveillance networks by participating in standard reporting of AMR and sharing AMR data
• Selected Infection Prevention Control (IPC) practices for prevention of emergence and spread of antimicrobial resistant microorganisms by hand hygiene, barrier precautions, biomedical waste management and prudent and appropriate use of antibiotics

**Figure 3** Steps to contain antimicrobial resistance

have been proposed to improve antibiotic use—a comprehensive program that incorporates multiple strategies and collaboration among various specialties within a given health-care institution. Computer-assisted software programs may be especially useful in implementing these comprehensive programs. The antimicrobial stewardship program has shown to improve appropriateness of antibiotic use and cure rates, decrease failure rates and reduce health-care-related costs. Presently, available data suggest that good antibiotic stewardship reduces rates of *Clostridium difficile*-associated diarrhea, MDR-GNB and VRE. **Box 3** shows the strategies of good antimicrobial stewardship.

BOX 3 Good antimicrobial stewardship strategies

- Education/guidelines for antimicrobial use: active methods work better than passive
- Formulary restriction: restrict dispensing of some antimicrobials to approved indications
- Review and feedback: daily review of targeted antimicrobials for appropriateness
- Computer-assisted strategies: using IT to implement previous strategies
- Antimicrobial cycling: scheduled rotation of antimicrobials used in a hospital or unit.

IN A NUTSHELL

1. Antimicrobial resistance is a global problem in the hospitals as well as in the community and is listed at the top of CDC list of emerging infectious threats to the public health.
2. Surveillance of AMR is required, which involves the systematic collection and analysis of health-related data and dissemination to those who will use them in decision-making on public health issues.
3. The antimicrobial stewardship program has shown to improve appropriateness of antibiotic use and cure rates, decrease failure rates and reduce health-care-related costs.
4. Every hospital should decide on appropriate antimicrobial stewardship programs so that AMR can be halted.

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Chapter 27.4

Infection Control and Prevention

Jaydeep Choudhury

Infections remain a leading cause of disease in most part of the world. Most of the infections are acquired in the community. Those infections which manifest among patients only after 48 hours of stay in hospitals are called *nosocomial* or *health-care-associated infections (HCAIs)*. The infection may manifest even after discharge to home. For obvious reason, the profile and severity of these infections are different than those acquired in the community. These infections lead to significant morbidity, mortality and economic burden, which is beyond those expected from the patients' underlying disease. As these infections are acquired under health-care, they are preventable.

MAGNITUDE OF THE PROBLEM

Nosocomial infections can occur as outbreaks or as sporadic cases. Outbreaks are highly visible; but sporadic infections are far more important. Most nosocomial infections originate from neonatal intensive care unit (NICU), pediatric ICU (PICU), hematology-oncology and neonatal surgery. In Western world, the nosocomial infection rate is 5–10 infections per 100 patient admissions; in the developing world, the rate can be 25% or more. The distribution of infections by anatomic site in acute care hospitals of developed countries is shown in **Table 1**. In developing countries, the bloodstream infections are less and gastrointestinal infections and postoperative wound infections are more common. Bloodstream and pulmonary infections carry the highest mortality rates (25–30%).

Table 1 Distribution of infection by anatomic site in developed countries

Site	Percentage (%)
Urinary tract	35
Postoperative wound	25
Bloodstream	10
Pneumonia	10
Others	20

PATHOGENESIS

Nosocomial infections can be *exogenous* or *endogenous*. In the former, the pathogens gain direct access to the patient from the environment, either animate or inanimate source and initiate disease. Endogenous infections are derived from the patient's own microflora. Primary endogenous infections refer to pathogens derived from patient's own normal flora. In secondary endogenous, the pathogen colonizes the patient, becomes part of the normal flora and subsequently causes infection. Primary endogenous infections are always sporadic.

Mode of Spread

Nosocomial infections are transmitted by contact, vehicles, air or vectors. Person-to-person transmission through the hands of hospital staff or patients is the most important mode. Infrequent hand-washing by overburdened staff and staff having contact with increased number of patients are the most important factors. Vehicles of transmission of nosocomial infection could be food,

water, intravenous solutions or blood and blood products. Medical equipment, contaminated thermometers and other devices are also equally important. Rodents and cockroaches are known vectors of infection.

Pathogens Involved

About 65–70% of pediatric nosocomial infections are bacterial, 50% are gram-positive and about 20% are gram-negative. The distribution varies according to the age of the patient, site of infection and prevailing pathogen in the hospital. Coagulase-negative *Staphylococcus* is particularly associated with infections related to intravascular catheters.

Children are at greater risk of viral infections. Respiratory syncytial virus and adenovirus cause outbreaks of nosocomial respiratory tract infection. Rotavirus and hepatitis A virus cause gastrointestinal tract infection. Varicella-zoster infection outbreak in NICU is also well documented.

PREVENTION OF NOSOCOMIAL INFECTIONS

Under any situation, more than 20% of all hospital-acquired infections can be prevented. Most of the interventions are simple, basic and related to individual health-care worker. Careful hand-washing, appropriate isolation, use of gloves when required and proper use of devices go a long way in the prevention of nosocomial infections. Other systemic issues that also require attention are as follows:

- Availability of soap and water at all times which should be placed in a convenient location for easy access
- Surgical patients should receive preoperative antibiotics (1–2 hours before incision, not greater than 2 hours and never delayed to one after incision)
- Isolation of patients with communicable disease. Various modes of isolation in different diseases are shown in **Table 2**.

Table 2 Isolation and precautions for infection control

Modes of isolation	Diseases	Methods
Strict isolation	Diphtheria, rabies	Single room, gown, gloves, mask. Hand-washing. Proper care of contaminated articles
Contact isolation	Bronchiolitis, conjunctivitis, MRSA	Single room, mask for close contacts. Gloves for touching infected area. Strict hand-washing. Proper care of contaminated articles
Respiratory isolation	Measles, whooping cough, meningococcal diseases	Single room, mask for close contacts. Strict hand-washing. Proper care of contaminated articles
Enteric isolation	Rotavirus, shigellosis, any diarrhea	Preferably single room, gowns if soiling, gloves for handling infective material. Strict hand-washing. Care of contaminated articles
Blood and body fluid precautions	Hepatitis B, HIV	Isolation not indicated, no masks, gloves for handling blood or body fluid. Gowns if soiling likely. Proper care of contaminated articles
Protective isolation	Immunosuppressed patients	Single room, gowns, gloves, mask. Strict hand-washing. Sterilized food and drink

Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; HIV, human immunodeficiency virus.

Infection Control Program

Health-care authority should take the initiative to develop a national or a regional program to support hospitals and health-care system in reducing the risk of HCAs. The program must focus on a definite objective consistent with the national or local health-care objectives. It should aim to develop and regularly update guidelines for health-care surveillance, prevention and practical application; facilitate access to materials essential for hygiene; monitor nosocomial infections; plan effective interventions; and train health-care professionals in infection control. Components of infection control are listed in **Box 1**.

Infection control practices can be placed in two categories, *standard precautions*, which must be applied to all patients at all times, regardless of diagnosis or infectious status and *additional precautions*, which are specific to modes of transmission of the disease.

BOX 1 Important components of infection control

- Basic measures for infection control
- Education and training of health-care workers
- Protection of health-care workers
- Routine practice for infection control—antisepsis and asepsis, antibiotic usage, handling and use of blood products, hospital waste management
- Surveillance
- Incidence monitoring
- Outbreak investigation
- Research.

Standard Precautions

Standard precaution includes simple, cheap and feasible measures like hand hygiene, environmental cleaning and waste handling. Strict adherence to these methods is the key to successful control of HCAI. Components of standard precautions are listed in **Box 2**.

BOX 2 Components of standard precautions for infection prevention

- Hand hygiene—hand-washing and antisepsis
- Use of personal protective equipment when handling organic materials, like blood or other body fluids, excretions and secretions
- Appropriate handling of patient care equipment and soiled linen
- Prevention of needle stick or sharp injuries
- Environmental cleaning and management practices
- Appropriate handling of waste
- Patient placement and transportation.

Hand Hygiene

Proper hand hygiene practices minimize microorganisms acquired on the hands during daily health work and when there is contact with blood, body fluids, secretions, excretions and contaminated equipment or surfaces. Hands should be washed in all the above situations and also in between attending patients. It is also important to wash hands after removing the gloves as gloves do not provide complete protection against hand contamination. The following are the indications for hand-washing with soap and water strictly for 2 minutes.

- At the entry of ICU (PICU, NICU)
- Before performing any invasive procedures before wearing gloves
- When hands are visibly soiled with dirt or organic material
- After touching soiled linen or other items, mucous membranes, wounds, dressings even if the hands are not soiled
- After examining a culture-proven sepsis patient
- Every time after removing gloves.

Alcohol-based hand rubs have been shown to be superior to soap in decreasing the bacterial colony counts. They are

recommended to be used after drying hands following hand washing and also routinely before and after every patient contact. Alcohol-based hand antiseptics are not effective on hands that are visibly dirty or contaminated with organic material unless they are first washed with soap and water.

Use of Personal Protective Equipment

Using personal protective equipment provides a physical barrier between microorganisms and the wearer. It offers protection by helping to prevent microorganisms from contaminating hands, eyes, clothing, hair and shoes and be transmitted to other patients and staff. Personal protective equipment include gloves, mask, gown, cap or hair cover, protective eye wear (goggles), apron, and boots or shoe covers. Personal protective equipment should be used by health-care workers who provide direct care to patients and support staff including medical aides, cleaners, laundry staff, who may have contact with patient's organic materials. It should also be used by laboratory staff who handle patient specimens and family members who provide care to patients.

Handling of Patient Care Equipment and Soiled Linen

Patient care equipment soiled with organic materials should be handled with care in order to prevent exposure to skin and mucous membranes, clothing and the environment. All reusable equipment should be cleaned and reprocessed appropriately before using on another patient. Used linen that is soiled with organic material should be handled with care to ensure that there is no leakage of organic fluid into the surrounding surface. The method and periodicity of decontamination depends on the equipment type and is shown in **Table 3**.

Prevention of Needle Stick/Sharps Injuries

Needles, scalpels and other sharp instruments or equipment should be used with utmost care. Used disposable syringes and needles, scalpel blades and other sharp items should be placed in a puncture-resistant container with a lid that closes. Extra care should be taken while cleaning sharp reusable instruments or equipment. Needles should never be recapped or bent. Sharps must be appropriately disinfected and/or destroyed as per the national standards or guidelines.

Patient Placement

Spacing between beds There should be adequate spacing between each bed to reduce the risk of cross infection due to direct or indirect contact or droplet transmission. Optimum spacing between beds is 1–2 meters.

Single rooms Single rooms reduce the risk of transmission of infection from the source patient to others by reducing direct or indirect contact transmission. Wherever feasible, single rooms should have hand-washing facilities and toilet facilities.

Cohorting If single rooms are not available, patients infected or colonized by the same organism can be cohorted. If cohorting is used during outbreaks, these room/s should be in a well-defined area (a designated room or designated ward), which can be clearly segregated from other patient care areas in the health-care facility used for noninfected patients.

Transportation of Patients

If transportation is required, suitable precautions should be taken to reduce the risk of transmission of microorganisms to other patients, health-care workers or the hospital environment. For example, while transporting an open case of pulmonary tuberculosis (TB), placing a surgical mask on the patient is an appropriate precaution.

Table 3 Patient care equipment and linen decontamination

Item	Activity	Periodicity
Incubators, warmers, trolleys	In use: detergent and water Not being used: 2% glutaraldehyde	In use: daily Not being used: dismantle weekly and clean with 2% glutaraldehyde
Ventilator body	2% carbolic acid	Once daily
Infusion pumps/monitors	Clean with moist cloth	Once daily
Ambu bag and accessories	Dismantle, wash visible contamination, then 2% glutaraldehyde for 30 minutes Dismantle, wash visible contamination, then 2% glutaraldehyde for 6 hours	After each use Once weekly
Rubber and plastic tubing	2% glutaraldehyde for 6 hours	Once daily
Humidity bottles, suction bottles and oxygen hoods	Clean with detergent	Once daily
Laryngoscopes	Clean with spirit 2% glutaraldehyde for 30 minutes	After each use Once daily
Thermometer, stethoscopes, measuring tapes	Wipe with spirit	Before and after each use
Weighing machines	Wipe with moist cloth	Once daily
Saturation probes	Preferably use disposable, while reusing wipe with spirit	Before and after each use
BP cuff	Ideally use disposable, while reusing wipe with spirit	Before and after each use
Procedure sets	Autoclave	After each use
Linen and gowns	Manually clean and then autoclave	After each use
Feeding utensils	Wash with detergent, boil for 20 minutes	Before each use

Environmental Cleaning and Management Practices

A clean environment plays an important role in the prevention of HCAI. Routine cleaning is important to ensure a clean and dust-free hospital environment. Most patient-care areas should be cleaned by wet mopping. The use of a neutral detergent solution improves the quality of cleaning. Areas visibly contaminate with blood or body fluids should be cleaned immediately with detergent and water. Isolation rooms and other areas that have patients with known transmissible infectious diseases should be cleaned with a detergent/disinfectant solution at least daily. All horizontal surfaces and all toilet areas should be cleaned daily.

Air ventilation Ventilation systems should be designed and maintained to minimize microbial contamination. The air conditioning filters should be cleaned periodically and fans that can spread airborne pathogens should be avoided in high-risk areas. High-risk areas such as operating rooms, critical care units and transplant units require special ventilation systems. Filtration systems (air handling units) designed to provide clean air should have high-efficiency particulate air (HEPA) filters in high-risk areas. Unidirectional laminar airflow systems should be available in appropriate areas in the hospital construction. Special air handling is needed for the operating room and for immunocompromised patients.

Handling of Waste

Hospital waste is a potential reservoir of pathogenic microorganisms and requires appropriate, safe and reliable handling. The main risk associated with infection is sharps contaminated with blood. There should be a person or persons responsible for the organization and management of waste collection, handling, storage and disposal. Waste management practices must meet national and local requirements. Steps in the management of hospital waste are described below:

Segregation and collection Infectious waste should be collected and segregated from noninfectious waste in dedicated containers

at the source. This prevents contamination by infectious waste to other hospital waste.

Transportation Waste should be transported in a dedicated trolley. They should be cleaned regularly.

Storage Waste should be stored in specified areas with restricted access. Sharps should be stored in sharps containers. Sharps containers should be made of plastic or metal and have a lid that can be closed. They should be marked with the appropriate label or logo, e.g., a biohazard symbol for clinical (infectious) waste.

Treatment Each health-care facility should identify a method for the treatment of infectious waste. This may consist of transportation of infectious waste to a centralized waste treatment facility or on-site treatment of waste.

Final disposal Sharps should be autoclaved after chemical treatment and landfill or microwave. Deep burial should be done in a secure area. Burial should be 2–3 meters deep and at least 1.5 meters above the groundwater table. Anatomical parts, animal carcasses, cytotoxic drugs (residues or outdated) and toxic laboratory chemicals other than mercury should be incinerated. Patient-contaminated nonplastics and nonchlorinated plastics may be also incinerated. Plastics, nonplastics contaminated with blood, body fluids, secretions and excretions and infectious laboratory wastes also should not be incinerated. Such wastes should be treated by steam sterilization in autoclavable bags or microwave treatment. Chemical treatment with 1% hypochlorite or a similar disinfectant is recommended. However, excessive use of chemical disinfectants should be avoided. Radioactive waste should be dealt with according to national laws. Treatment and final disposal of waste is shown in **Table 4**.

Additional Precautions

Airborne Precautions

Airborne precautions are designed to reduce the transmission of diseases spread by the airborne route. Airborne transmission

Table 4 Treatment and final disposal of waste

Color coding	Waste	Treatment and final disposal
Yellow (solid infectious)	Human tissues, organs, body parts Microbiology and biotechnology waste (wastes from lab cultures, specimens, live-attenuated vaccines, etc.) Waste items contaminated with blood and body fluids including cotton dressings, soiled plaster casts, linen	Incineration
Red (solid noninfectious)	Waste generated from disposable items other than sharps like tubings, catheters, IV sets	Disinfect by chemical treatment (1% hypochlorite) then either autoclave and later shredding
Blue (sharps)	Needles, syringes, scalpel blades, glass, etc.	Disinfect by chemical treatment (1% hypochlorite) then either autoclave and later shredding
Black (other wastes)	Discarded medicines and left-over foods	Taken for landfill

occurs when droplet nuclei (evaporated droplets) less than 5μ in size are disseminated in the air. These droplet nuclei can remain suspended in the air for a long time. Diseases which spread by this mode include open/active pulmonary TB, measles, chicken pox and other viral infections.

Droplet Precautions

Droplets are usually generated from the infected person during coughing, sneezing, talking or when health-care workers undertake procedures, such as tracheal suctioning. Droplet transmission occurs when there is adequate contact between the mucous membranes of the nose and mouth or conjunctivae of a susceptible person and large particle droplets ($> 5\mu$). Diseases, which are transmitted by this route include viral and bacterial pneumonias, pertussis, diphtheria, influenza type B, mumps and meningitis. In these cases, patients should be placed in a single room (or in a room with another patient infected by the same pathogen). Health-care persons should wear a surgical mask.

Contact Precautions

Diseases which are transmitted by this route include colonization or infection with multiple antibiotic-resistant organisms, enteric infections and skin infections. Here patient should be placed in a single room (or in a room with another patient infected by the same pathogen). Clean, nonsterile gloves and gown should be used when entering the room. Limit the movement and transport of the patient from the room; patients should be moved for essential purposes only. If transportation is required, use precautions to minimize the risk of transmission.

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IN A NUTSHELL

1. Infections which manifest among patients only after 48 hours of stay in hospitals are called *nosocomial* or *HCAIs*.
2. These infections lead to significant morbidity, mortality and economic burden.
3. Most of the nosocomial infections are present in NICU, hematology-oncology and neonatal surgery.
4. Nosocomial infections are transmitted by contact, vehicles, air or vectors.
5. About 65–70% of pediatric nosocomial infections are bacterial, 50% are gram-positive and about 20% are gram-negative.
6. More than 20% of all hospital-acquired infections can be prevented. Most of the interventions are simple, basic and related to on individual health-care worker.
7. Hand-washing is the single most important step for prevention.
8. Hospital waste is a potential reservoir of pathogenic micro-organisms and requires appropriate, safe and reliable handling.

Section 28 FEVER

Section Editor Piyush Gupta

Chapter 28.1

Approach to a Child with Fever

Bhavna Dhingra, Piyush Gupta

Fever, in common parlance, is an elevation of body temperature above normal, but not all causes of temperature elevation constitute fever (e.g., heat stress and heat illness). Fever is an elevation of core body temperature as part of a specific biological response, mediated by cytokines and controlled by the central nervous system (CNS). It is a characteristic feature of many diseases, both infectious and noninfectious, and it involves activation of various physiological, endocrinological and immunological systems.

Normal body temperature follows a circadian rhythm and varies between 36.6°C in the morning to 37.9°C in the evening. Body temperature is controlled by the thermoregulatory center located in the preoptic anterior hypothalamus, which balances heat production, derived primarily from metabolic activity in muscle and the liver, with heat dissipation from the skin and lungs to maintain the temperature in a steady range. Oral temperature is generally 0.6°C (1.0°F) lower than rectal temperature because of mouth breathing, which is particularly important in patients with respiratory infections and rapid breathing. Lower esophageal temperature reflects core temperature, and tympanic membrane (TM) temperature readings also approximate to core temperature. Beyond the newborn period, infants and young children generally have higher body temperatures due to the greater surface area to body weight ratio and the higher metabolic rate than older children and adults.

DEFINITION

A clinically significant fever is generally defined as a rectal temperature of 38°C (100.4°F) or higher. This is equivalent to an oral temperature of 37.5°C (99.5°F), and axillary (armpit) temperature of 37.2°C (99°F). Fever above 41.5°C (107°F) is called hyperpyrexia and may lead to irreversible organ damage.

PATHOPHYSIOLOGY OF FEVER

Fever is induced by pyrogens. Bacteria, fungi, viruses, malignancies, connective tissue disorders, certain drugs, and trauma may endogenously stimulate production of pyrogens.

- Common *endogenous pyrogens* include interleukin 1 (IL-1), tumor necrosis factor (TNF) and interferon. Other endogenous pyrogens include IL-6, IL-11, leukemia inhibitory factor (LIF), ciliary neurotropic factor (CNTF) and oncostatin-M. Large amounts of IL-6 circulate in nearly all febrile diseases, and IL-6, induced by IL-1 or by the combination of IL-1 and TNF, accounts for most clinical fevers.
- *Exogenous pyrogens* include the bacterial cell wall component lipopolysaccharide (LPS), enterotoxins, and exotoxins. Exogenous pyrogens can induce production of endogenous pyrogens via activation of Toll signaling, and both endogenous and exogenous pyrogens stimulate the synthesis of prostaglandins (PG).

Prostaglandin E2 (PGE2) is the ultimate endogenous pyrogen. It resets the temperature of the hypothalamus.

Fever is the result of a series of events that begins peripherally with the synthesis and release of IL-1 and other cytokines by phagocytic cells in the blood or tissues. **Flow chart 1** illustrates the pathophysiology of fever.

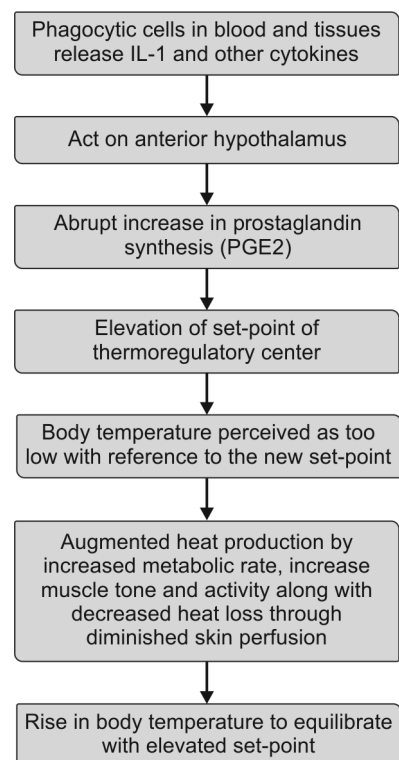
ADVANTAGES OF FEVER

The survival of some pathogenic bacteria or viruses is impaired at temperatures in the range of 40°C (104°F). Many pathogenic bacteria require iron for their growth, and fever is associated with a decrease in serum iron and a simultaneous increase in the iron-binding protein, ferritin, resulting in low levels of free iron in the blood. It has been suggested that this response is a coordinated host defense mechanism meant to deprive bacteria of free iron. Enhancement of several human immunologic functions occurs at moderately elevated temperatures, e.g., increased lymphocyte transformation response to mitogen, increased bactericidal activity of polymorphonuclear leukocytes, and increased production of interferon with increasing temperature. Beyond 40°C, most of the functions decline below baseline levels.

DISADVANTAGES OF FEVER

Fever is associated with an increased metabolic rate, increased oxygen consumption, increased carbon dioxide production, and

Flow chart 1 Pathophysiology of fever



increased demands on the cardiovascular and pulmonary systems. Fever often makes patients uncomfortable. Fever can precipitate febrile convulsions in children between 6 months and 5 years of age. Fever can aggravate cerebral injury.

ETIOLOGY OF FEVER

Fever is probably the most common presenting complaint in pediatric practice and is associated with a wide variety of illnesses. The most common cause of fever in children is a viral infection. In viral infection, fever is usually short-lived and signs are usually more generalized than those with bacterial infection. Common viral and bacterial illnesses like upper respiratory infections (URI), gastroenteritis, ear infections, croup, and bronchiolitis are the most likely illnesses known to cause fevers of short duration. Viral fevers usually resolve in about a week, persistence of fever beyond this time requires a detailed work-up. Bacterial URIs may be difficult to distinguish from viral URIs but the presence of pus points in the tonsil and unilateral involvement of ears points towards a bacterial etiology. Other common infective causes that need to be looked into are malaria, urinary tract infections, sepsis, abscesses, etc.

EVALUATION OF A FEBRILE CHILD

Performing a detailed and thorough history and physical examination is the first and most important component of the diagnostic evaluation of a febrile child. The next steps are to (i) localize the fever to a particular organ system by presenting complaints; and to (ii) identify the probable etiology of fever, depending upon its duration, pattern and clinical examination.

History

The history should include questions regarding characteristics of fever (onset, intensity, duration, frequency and pattern of fever—continuous, remittent or intermittent); how was the temperature assessed—perceived manually or documented by a thermometer along with the site of documentation; localizing symptoms of fever; recent exposures like vaccination, animal/insect bites, or receipt of blood transfusion or biological product; exposure to a family member with fever or any infectious disease; past history of any significant illnesses such as tuberculosis, urinary infections, congenital heart disease, and surgical procedure; any history of travel in the recent past; history of an underlying chronic disease, and medication history. History of recurrent episodes of fever may give a clue to certain cyclic causes of fever. Ask for other system-related symptoms. Enquiry about specific symptoms may help in localizing the disease to a particular system.

Examination

The physical examination should begin with a general assessment of the patient's appearance, activity, vital signs, and growth parameters. It is a good idea to evaluate the child during febrile period as the presence or absence of few signs during the febrile phase may provide certain clues to diagnosis, e.g., absence of sweating in anhidrotic ectodermal dysplasia. Absence of malaise or other generalized signs in a child with a history of high fevers can signal factitious fever.

Identify the Etiology of Fever

Short duration fever Fever of less than 2 weeks duration is usually infectious in origin, and due to viruses, bacteria or protozoa. Many of these patients recover completely, even before a precise diagnosis is made or treatment is given. These children may present with or without localizing manifestations. Every effort should be made to identify and localize the system involved, based on the localizing symptoms, as shown in **Table 1**.

Table 1 Determining etiology of fever based on presenting features

<i>Cough and coryza</i>	<i>Viral fever</i>
Rash	Exanthematous illnesses like measles, rubella, chickenpox, erythema infectiosum, roseola infantum, herpes simplex; other illnesses like meningococemia, dengue, Henoch-Schönlein purpura, leukemia, and Kawasaki disease
Ear pain	Acute suppurative otitis media (ASOM)
Skin boils	Abscess, pustules, cellulitis, impetigo
Seborrheic dermatitis (± ear discharge)	Langerhans cell histiocytosis
Periungual desquamation with strawberry tongue	Kawasaki disease
Throat pain, difficulty in swallowing, cervical nodes	Pharyngotonsillitis
Stridor, dysphonia	Laryngitis, tracheitis, croup, epiglottitis, diphtheria
Fast breathing and cough, wheezing, chest in drawing, chest pain	Pneumonia, bronchiolitis, pleural effusion, tuberculosis
Joint swelling, pain or limited movements	Septic arthritis, rheumatic fever, tubercular arthritis, connective tissue diseases
Vomiting	Gastritis, gastroenteritis, viral hepatitis, meningitis, enteric fever, UTI
Diarrhea	Gastroenteritis, enteric fever, dysentery
Jaundice	Hepatitis, cholecystitis, malaria
Pallor, rash, bleeding, lymphadenopathy	Leukemia, infectious mononucleosis
Urinary frequency, burning micturition, crying during micturition, hematuria	Urinary tract infection, cystitis
Chills or pallor or jaundice	Malaria, hepatobiliary causes
Altered sensorium, seizures, neurological deficits, meningeal signs	Meningoencephalitis (bacterial, viral, tubercular), cerebral malaria, enteric encephalopathy, brain abscess
Abdominal pain	Gastroenteritis, appendicitis, liver abscess, hepatitis, cholecystitis, cholangitis, intra-abdominal/pelvic abscess, pyelonephritis

Prolonged fever Fever lasting for more than 2 weeks requires a different approach. Infections still remain the most important cause of prolonged fever; however, noninfectious causes are also responsible. Common causes of prolonged fever are listed below:

- **Infections:** Tuberculosis, HIV, urinary tract infections, chronic fungal infections, etc.
- **Inflammatory disorders:** Rheumatoid arthritis, systemic lupus erythematosus, Kawasaki disease and other connective tissue disorders including polyarteritis nodosa, Behcet disease, Wegner granulomatosis.
- **Malignancies:** Lymphoma (including Hodgkin disease), leukemia, hepatoblastoma, Wilms tumor, neuroblastoma, brain tumors.
- **Endocrine causes:** Thyrotoxicosis, diabetes insipidus.
- **Hematological and immune deficiency disorders:** Spherocytosis, agranulocytosis, hemolytic anemia; Langerhans cell histiocytosis, disorders of T- or B-cells; disorders of phagocytosis.

- *Neurologic disorders:* Familial dysautonomia, hypothalamic and third ventricle lesions; anhidrotic ectodermal dysplasia.
- *Miscellaneous causes:* Drug fever, periodic fever, factitious fever.

Box 1 provides a detailed list of common causes of fever associated with hepatosplenomegaly, rash, or lymphadenopathy. When fever has been persistent for a week, and no cause has been

BOX 1 Etiology of fever with rash, lymphadenopathy and hepatosplenomegaly

Fever with Hepatosplenomegaly

- *Infectious causes:* Malaria, enteric fever, kala-azar, tuberculosis, infectious mononucleosis, brucellosis, echinococcosis, rickettsial diseases, TORCH infections, dengue, septicemia, and infective endocarditis
- *Malignancies:* Leukemias, lymphomas, histiocytosis, infantile heman-gioendothelioma, hepatoblastoma, and metastases
- *Connective tissue diseases:* Systemic lupus erythematosus (SLE); systemic juvenile idiopathic arthritis (JIA), sarcoidosis, scleroderma, and rheumatic fever
- *Chronic hepatitis/chronic liver disease:* Autoimmune hepatitis, chronic hepatitis B/C, and Wilson disease.

Fever with Rash

- *Infectious causes:* Meningococemia, dengue, measles, rubella, varicella, roseola infantum, erythema infectiosum, herpes simplex, and lupus vulgaris
- *Malignancies:* Leukemia and histiocytosis
- *Vasculitis:* Henoch-Schönlein purpura, Kawasaki disease, rheumatic fever, systemic JIA, and SLE.

Fever with Lymphadenopathy

- Suppurative lymphadenitis (bacterial, often accompanying pharyngitis, tonsillitis, dental infections, scalp infections)
- Tuberculosis
- Lymphoma (Hodgkin and non-Hodgkin lymphomas)
- Histiocytosis
- Acute lymphoblastic leukemia (ALL)
- HIV infection
- Connective tissue disorders such as systemic JIA or sarcoidosis
- Kawasaki disease
- Rosai-Dorfman disease.

found, serious consideration should be given to hospital admission to confirm pyrexia and initiate investigations. Appropriate laboratory testing as per the merit of each case may include: complete blood counts with peripheral smear, ESR, CRP, urinalysis and urine culture, blood cultures and serologic tests when appropriate (e.g., for enteric fever, malaria, dengue, leptospirosis, TORCH infections, rickettsial infections, *Coccidioides immitis*, *Cryptococcus neoformans*, *Borrelia burgdorferi*, *Treponema pallidum*, and HIV). Radiological investigations may include X-ray chest; ultrasonography, CT and MRI, as indicated. Other common though invasive investigations include bone marrow examination, lumbar puncture, cytopathology, and examination of ascitic/pleural/joint fluids.

IN A NUTSHELL

1. Fever is a symptom of an underlying disease, which may be infective or noninfective.
2. Fever results due to a change in the set point of hypothalamic thermoregulatory center.
3. The most common cause of fever in the young child is usually a self-limiting viral infection.
4. A detailed and thorough history and physical examination is the most important component in the evaluation of a febrile child.
5. Duration of fever and associated symptoms aided by appropriate investigations can help in localizing cause of fever.

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Chapter 28.2

Fever: General Principles of Management

Piyush Gupta, Bhavna Dhingra

All fevers do not need to be treated, and when treated, the primary objective of treating fever should be to make the child comfortable, and not the normalization of body temperature. Antipyresis can be achieved by nonpharmacological measures and/or drugs. Antipyretics may help in overall management of a febrile child but do not appear to affect the recurrence of febrile seizures.

NONPHARMACOLOGICAL ANTIPYRESIS

Nonpharmacological methods include environmental modifications, increased fluid intake, and mechanical cooling.

Environmental Modifications

Place the child in cool and airy environment (21–22°C) which enhances heat loss by convection. Minimal clothing; i.e., dressing the child in only one layer, is advocated to enhance heat loss. Some theories support a gentle body massage to dilate the cutaneous blood vessels which further increases heat dissipation.

Hydration

As fever increases, the metabolic rate of the body also goes up. For each 1°C rise of temperature above 37.2°C, there is an increase in insensible water loss of 7 mL/kg body weight/day. Hence, extra fluid intake is advised in febrile patients. For each 1°C of increase in temperature, a 12% increase in fluid intake is recommended.

Mechanical Cooling (Hydrotherapy or Sponging)

It is considered the mainstay of nonpharmacological antipyresis. External cooling lowers the temperature of febrile patients by evaporation, conduction, and convection. Evaporation is rated as the most effective physical mean of promoting heat loss in febrile children because it has the least capacity to induce shivering. External cooling acts by impairing the overwhelming effect or mechanisms evoked by elevated thermoregulatory set point, rather than by lowering the elevated set point. The capacity of external cooling to lower core temperature is limited because it induces both cutaneous vasoconstriction and shivering. Therefore, unless concomitant antipyretic therapy or other pharmacological methods are used to abolish shivering, external cooling is vigorously opposed in febrile patients by thermoregulatory mechanisms endeavoring to maintain elevated temperature.

External cooling with ice is the treatment of choice for heatstroke and other forms of heat illness, but is more discomforting. For fever, external cooling is indicated only in specific situations, and with tepid rather than cold water. Some infants with infection may also have a component of heat illness from over-wrapping, dehydration, or drugs such as atropine. Sponging should be done by continuous wiping of the body with tepid water (28–30°C) from head to toe for 15–20 min. Sponging action ensures that water film is constantly moving thus maximizing heat conduction. Tepid sponging acts by conduction of heat from the warm skin to water. An absorbent towel should be soaked, rinsed and placed on the legs, trunk and forehead in order to reduce the body temperature. Hydrotherapy should be continued till the body temperature comes down to 38°C. Indications for sponging is summarized in **Box 1**. Studies indicate that hydrotherapy alone is clearly inferior to antipyretics for reduction of fever for periods longer than

BOX 1 Indications for sponging with lukewarm water in fever

- Febrile delirium
- Febrile seizure
- Fever > 41.1°C
- Patients with neurologic disorders, because many of these children have abnormal temperature control and respond poorly to antipyretic agents
- Children with hypersensitivity to antipyretic agents
- Children with severe liver disease.

30 min after initiation of treatment. External cooling may, however potentiate the activity of antipyretics.

Results of randomized trials comparing the combination of antipyretics and physical methods with antipyretics alone have provided mixed results. In 4 out of 7 such studies the combination treatment was superior to use of antipyretics alone for reduction of temperature during first 30 min of initiation of therapy and overall. In other 3 studies both modes of treatments were equally effective in lowering temperature. It is recommended to administer antipyretic drugs at least 30 min before sponging.

The main disadvantage of hydrotherapy is patient discomfort and shivering. Shivering not only impedes cooling during fever but also imposes considerable metabolic burden. Studies in volunteers have shown that shivering increases the oxygen consumption, respiratory minute volume, respiratory quotient, increase in percentage of carbon dioxide in exhaled air during exposure to cold and increase in mean arterial pressure. Perhaps in febrile patients with cardiovascular disease external cooling can cause coronary artery vasoconstriction by cold press or response and thus decrease coronary perfusion. Sponging, though rapid in reduction of temperature, has an ill sustained effect.

PHARMACOLOGICAL ANTIPYRESIS

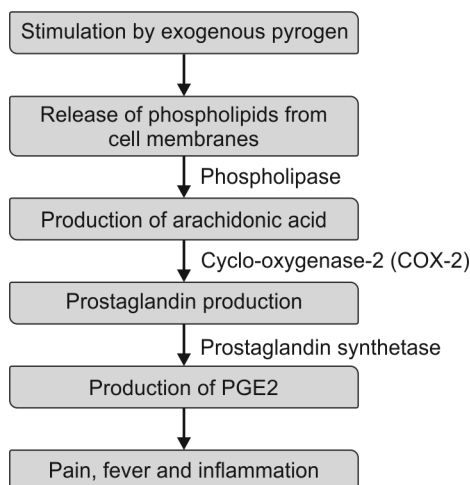
Antipyretic agents are administered to provide symptomatic relief in children with fever. Keeping in mind that fever results from change in the set temperature of the hypothalamic thermoregulatory center, it seems logical to bring down the temperature by restoring the hypothalamic set-point to normal.

Commonly used agents to achieve antipyresis include paracetamol, ibuprofen, and aspirin. Aspirin was the first antipyretic used in children. However, after reports of its association with causation of Reye syndrome, aspirin is not recommended for controlling fever in children. Mefenamic acid and nimesulide are the other drugs used infrequently to control fever.

Mechanism of Action

The antipyretic medications act via the arachidonic acid pathway (**Flow chart 1**). Arachidonic acid is a substrate for both cyclooxygenase-2 (COX-2) and a second isoform of the enzyme, COX-1. COX-2 is the principal mediator of the inflammatory response, resulting in production of prostaglandin₂ (PGE₂). COX-1 products, on the other hand, function primarily in renal function, vascular homeostasis and gastrointestinal cytoprotection. Central inhibition of COX is responsible for the antipyretic effects of paracetamol. Relatively weaker inhibition of splenic COX accounts for its relatively poor anti-inflammatory response. Paracetamol is nearly as effective as aspirin and 10% as effective as indomethacin in inhibiting central COX but only 5% as effective as aspirin and 0.02% as effective as indomethacin in inhibiting peripheral COX.

Ibuprofen is a competitive inhibitor of the COX enzymes, in that it competes with arachidonic acid for binding to the catalytic site on COX, thereby preventing prostaglandin synthesis. This is a reversible process. Unlike paracetamol, ibuprofen acts peripherally and lacks specificity for either COX isomer. Ibuprofen therefore has antipyretic, analgesic and anti-inflammatory actions.

Flow chart 1 The arachidonic acid metabolism pathway

Dosing and Toxicity

Paracetamol

Paracetamol is recommended in a dose of 15 mg/kg at 4–6 hourly intervals not exceeding 60 mg/kg/day. Antipyretic effect begins within 30–60 min, approximately 80% of children will experience a decreased temperature within this time frame. Paracetamol reduces the temperature by 1–2°C after 2 hour of intake. The rate of fall of temperature is directly related to the degrees above which initial temperature was above baseline. Greater the initial temperature, greater is the fall after drug intake and vice versa. Hence, drug administration in low grade temperature may not lead to any significant fall and antipyretic treatment in high grade fevers (> 104°F) would result in reduction of temperature by less than 1°C, failing to touch the baseline.

Ibuprofen

Ibuprofen can also be used as a first line antipyretic. Efficacy of paracetamol and ibuprofen has been compared in a number of studies, and some have shown greater antipyretic effect with 10 mg/kg of ibuprofen as compared to 15 mg/kg of paracetamol. Ibuprofen has the advantage of longer duration of antipyresis (8 h) as compared to paracetamol (4 h). Recent evidence indicates that there is no difference in the safety and effectiveness of paracetamol and ibuprofen in the care of a generally healthy child with fever. There is evidence that combining these 2 drugs is more effective than using them alone. However, this should not be followed as a routine because of associated risk of inappropriate dosages. The practice of alternating ibuprofen and paracetamol has limited value.

Nimesulide

Nimesulide has a superior efficacy when compared to paracetamol, aspirin, naproxen and mefenamic acid. Also the advantage of reduced frequency of dosing (2–3) exists with its use. However, use of nimesulide in children is associated with potentially fatal adverse effects resulting in hypothermia, hepatotoxicity, and renal damage.

Mefenamic Acid

Mefenamic acid is a reversible competitive inhibitor of COX-1 and COX-2 enzymes and has analgesic, antipyretic, and anti-inflammatory properties. It is very effective in control of high fever in a dose of 6–7 mg/kg/dose (20 mg/kg/day in three divided doses), usually a single dose suffices and can later be followed by paracetamol after 6–8 hour. Its main side effects are diarrhea, hemolytic anemia, thrombocytopenia and drowsiness.

Choice of Antipyretic

The decision regarding the choice of antipyretic should be based on personal experience, scientific data regarding efficacy, safety, duration of effect, and cost. In therapeutic dosages aspirin is more toxic and causes gastritis, gastrointestinal bleeding, impaired platelet function, diminished urinary excretion of sodium, Reye syndrome and blunted immune response. These side effects are known to occur less frequently with ibuprofen and none with paracetamol. Paracetamol can be safely used in children with asthma, with sensitivity to aspirin or ibuprofen, coagulation disorders, peptic ulcer or reflux esophagitis. Thus paracetamol is considered to be the safest antipyretic in children at therapeutic dosages. Hepatotoxicity appears to be the most serious and well-documented toxicity associated with use of paracetamol in children. Concern has been raised over the gastrointestinal disturbance and nephrotoxicity with ibuprofen; hence caution is encouraged when using ibuprofen in children with dehydration. In the overdose situation, the toxicity of paracetamol is not only reached much earlier, but is also more severe and more difficult to manage as compared with an overdose of ibuprofen.

The most commonly used and preferred mode of administration of antipyretics is the oral route. Rectal suppositories may be used in children with febrile seizures or unconscious patients. Parenteral (intramuscular or intravenous) administration of paracetamol may be used in cases where quick relief of fever is required or when oral administration is not possible, e.g., comatose children. The dose of intravenous paracetamol is 7.5 mg/kg/dose (max. 30 mg/kg/day) for neonates and infants and 15 mg/kg/dose for older children (max. 60 mg/kg/day) to be given as an infusion.

Parental Education

Fever is the most common complaint for which medical attention is sought by the caregivers. It also causes considerable parental anxiety and concern; therefore, appropriate counseling of parents and caregivers is a must. Parents need to be explained that fever is a protective response of body and helps to fight the disease. Medical personnel need to emphasize and deal with issues, such as what is fever, what is high grade fever, advantages and disadvantages of fever, when and which fever should be treated and how, the danger signs associated with fever, and when to seek medical help.

HEAT HYPERPYREXIA

Heat hyperpyrexia is not an unusual cause of fever in tropical countries where ambient temperature may go as high as 45°C. Heat hyperpyrexia may occur even without exposure of the child to the direct sunlight. The predisposing factors include high temperature and humidity in the environment, unsuitable clothing, dehydration and debilitating illness, such as malaria, pneumonia, measles, and renal disorders. Invariably, heat hyperpyrexia is associated with cessation of sweating. Children with ectodermal dysplasia and absence of sweat glands are more prone to develop episodes of heat hyperpyrexia.

The onset of high fever may be quite sudden. The rectal temperature may exceed 42°C to 43°C. The skin appears hot and dry (without sweating). Tachycardia and tachypnea are present. The loss of consciousness occurs early. The patient may develop peripheral circulatory failure and hemorrhages. Headache, faintness, abdominal discomfort and delirium are usually complained of. The liver and kidney failure may complicate heat hyperpyrexia.

Management

When the temperature exceeds 41°C, body of the child below the neck should be immersed in the cold water without further delay to prevent irreversible brain damage. The parents should be reassured that this seemingly drastic measure will not induce shock. Ice cold bath does not cause significant vasoconstriction. The rectal temperature should be recorded continuously and the hydrotherapy should be discontinued as the temperature falls below 38°C.

IN A NUTSHELL

1. Fever *per se* is just a symptom of underlying illness and not a disease itself.
2. All fevers do not need treatment. The aim of treating fever is not normalization of body temperature.
3. Febrile children should be advised to drink plenty of water and wear loose comfortable clothing.
4. Medicines should be used only when indicated. Paracetamol (15 mg/kg) is the safest antipyretic in children. Ibuprofen is an alternative. Aspirin and nimesulide should not be used in children.
5. Hydrotherapy with tepid water may be useful when used in combination with pharmacological antipyresis.
6. Explain to parents that febrile seizures occur in minority of children, are benign and do not cause any permanent brain damage or epilepsy.
7. Close monitoring is required in children with past history of febrile seizures.
8. Parents should be taught the emergency management of febrile seizures.

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Chapter 28.3

Fever without Focus

Piyush Gupta, Bhavna Dhingra

Fever without focus in a child is defined as a rectal temperature of 38°C or higher as the only presenting symptom and can be sub-categorized into *fever without localizing signs* (FWLS) and *fever of unknown origin* (FUO).

FEVER WITHOUT LOCALIZING SIGNS

Children presenting with history of acute onset of short duration fever (usually less than a week) as the only presenting complaint without any signs or symptoms localizing to any organ system are categorized as having fever without localizing signs. This presents a diagnostic challenge in children less than 36 months of age. These children represent an important group because of higher risk of occult bacteremia and serious bacterial infections (SBI) (range 5–20%). Therefore, it may sometimes become essential to start specific and empirical treatment without establishing an etiological diagnosis. As the etiology of this entity and risk of SBI is variable in different age groups, these children are usually subclassified into the following three categories:

1. Neonates (up to 1 month of age).
2. Infants, 1–3 months of age.
3. Infants, 3–36 months of age.

There are certain high-risk groups of children who are at increased risk of SBI and require a more aggressive outlook. These include children presenting with: hyperpyrexia (> 40°C); fever with petechiae; and immunocompromised patients with asplenia, sickle cell disease, complement deficiency states, agammaglobulinemia, hypogammaglobulinemia, congenital heart disease, malignancy, or AIDS.

Neonates (Birth-1 Month of Age)

Newborns presenting with fever without localizing signs present a diagnostic dilemma for the treating clinician. They have a very limited number of signs of infection and that too are nonspecific. Immune response is also not mature. It is difficult to differentiate between dehydration fever, a self-limited viral illness, and SBI. SBI ranges from occult bacteremia, pneumonia, meningitis, urinary tract infection, and enteritis, to osteomyelitis, and septic arthritis.

Any newborn or young infant presenting with fever should be hospitalized and after control of ambient environmental temperature and adequate hydration with increased frequency of breastfeeding, if the baby is still febrile—possibility of SBI should be entertained even in an apparently healthy neonate. All such neonates should be subject to a septic screen which includes complete blood counts with band form count, urine microscopy, blood culture, urine culture, chest X-ray, and peripheral smear for malarial parasite. Lumbar puncture and cerebrospinal fluid analysis (cell counts, glucose, protein, Gram stain and culture) should be undertaken in children with lethargy or refusal to breastfeeding.

Etiology

Haemophilus influenzae B and *Streptococcus pneumoniae* are the two most important causes of SBI in India, besides *Klebsiella*, *Staphylococcus aureus*, and *Escherichia coli*. *Listeria monocytogenes* and perinatally acquired *Herpes simplex virus* (HSV) infection have also been implicated. Malaria should also be considered a strong possibility in endemic areas.

Management

After obtaining relevant investigations, empirical antibiotic therapy should be initiated at the earliest with combination of ampicillin and cefotaxime or monotherapy with ceftriaxone (100 mg/kg per day) and modified later as per the reports of the sepsis screen and cultures.

Fever in the Young Infant 1–3 Months of Age

Self limited seasonal viral illnesses are the most common cause of fever without localizing signs in this age group. The possibility of SBI should always be entertained in any febrile child between 1 month and 3 months of age and the following conditions should be ruled out: otitis media, pneumonia, skin and soft tissue infections, omphalitis and urinary tract infections especially in uncircumcised boys and children with urinary tract anomalies.

Risk Stratification

Febrile infants less than or equal to 3 months with diminished spontaneous activity, lethargy, respiratory compromise (tachypnea, chest retraction and grunting), diminished muscle tone, mottled cool extremities, irritability, weak sucking are at high-risk. Infants 1–3 month of age with fever who appear well and had been previously healthy, and have a normal physical examination, can be categorized as at *low-risk* or *high-risk* for serious bacterial infections by certain investigations. **Table 1** lists the various criteria used for identifying children 1–3 months at low-risk of SBI.

Etiology

The most common implicated organisms are Group B *Streptococcus*, *E. coli*, *S. aureus*, *S. pneumoniae*, *H. influenzae*, *Neisseria meningitidis* and enterococci. Pyelonephritis is the most common SBI and may be seen in well appearing as well as ill appearing children between 1 month and 3 months of age presenting with fever without localizing signs.

Management

Febrile children, 1–3 months of age who present with fever without localizing signs must be evaluated for sepsis by complete blood count, lumbar puncture, blood culture, urinalysis, urine culture and chest radiograph. Ill appearing infants require immediate hospitalization and prompt institution of empirical parenteral antimicrobial therapy. Ampicillin with either cefotaxime or ceftriaxone is an effective combination. Vancomycin should be included if possibility of meningitis with penicillin resistant *S. pneumoniae* is suspected. Antimicrobials can be modified as per the culture and sensitivity reports.

In well appearing infants a watchful observation without antibiotics may be planned and a sepsis screen obtained, although a lumbar puncture may be deferred. A mandatory follow-up after 24 hours must be ensured. Prior to initiation of antibiotics in the event of clinical deterioration, a lumbar puncture should always be done.

Fever without Localizing Signs in 3–36 Months Old Children

Viral infections are responsible for majority of children having nonlocalizing fever in this age group. Serious bacterial infection can also occur due to *S. pneumoniae*, *Neisseria*, and *H. influenzae*. Risk factors for occult bacteremia in these children include rectal temperature > 39°C, WBC counts > 15000/mm³, raised ESR, and elevated C-reactive protein. Rectal temperature > 40°C and WBC count > 25000/mm³ indicate a higher probability of serious bacterial infection. Important bacterial infections include otitis media, pneumonia, sinusitis, enteritis, urinary tract infection,

osteomyelitis and meningitis. Pneumococcal bacteremia can resolve spontaneously in about one-third of cases or can lead to development of localized infections, e.g., meningitis, pneumonia, cellulitis, pericarditis, osteomyelitis or septic arthritis. Management options are detailed in **Flow chart 1**. Infants with moderate to high

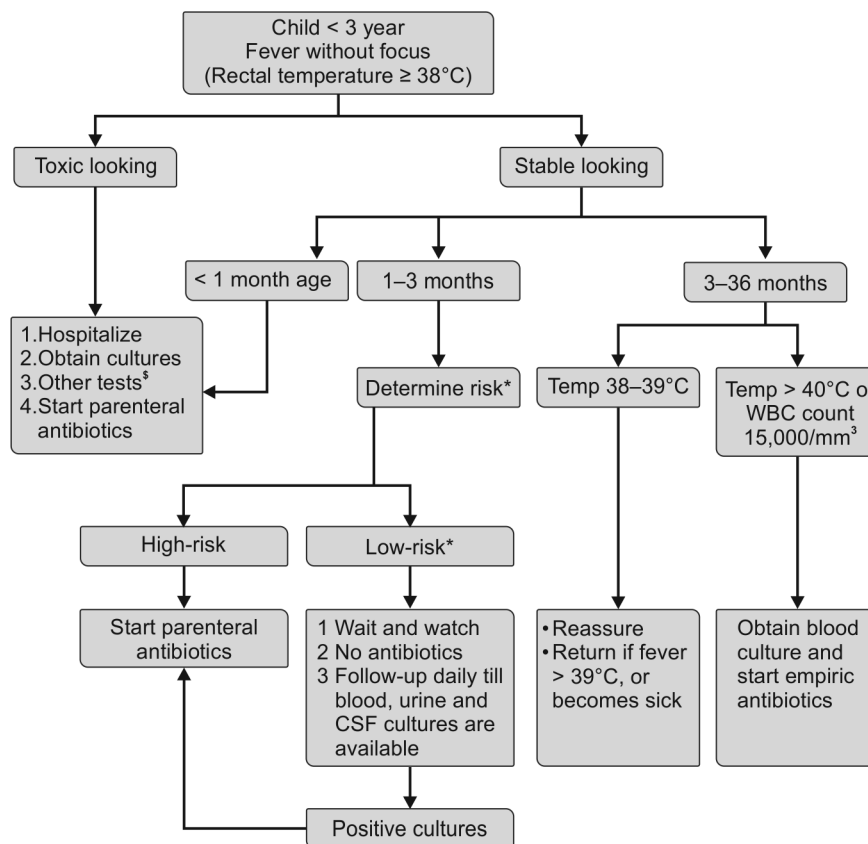
risk factors should be treated with ceftriaxone (50–80 mg/kg/day in one or two divided doses IV or IM). In infants below 4 weeks of age, ampicillin (50–100 mg/kg/day IM or IV two divided doses) should also be added to cover *Listeria monocytogenes* and enterococci, which are not sensitive to ceftriaxone.

Table 1 Low-risk criteria in 1–3 months old children with fever without localizing signs

	<i>Philadelphia protocol</i>	<i>Pittsburgh guidelines</i>	<i>Rochester criteria</i>	<i>Boston criteria</i>
General appearance	Well	Well	Well	Well
Physical examination	Normal	Normal	Normal	Normal
Complete blood count WBC/mm ³	< 15,000	5000–15000	5000–15000	< 20,000
I:T neutrophil ratio absolute band count	< 0.2	< 1500/mm ³	< 1500/mm ³	
Urine examination	< 10 WBC/HPF No bacteria on Gram stain	9 WBC/mm ³ No bacteria on Gram stain	< 10 WBC/HPF at 40X	Negative leukocyte esterase
Cerebrospinal fluid (If bloody tap)	< 8 WBC/mm ³ No bacteria on Gram stain	5 WBC/mm ³ No bacteria on Gram stain WBC:RBC ≤ 1:500		< 10 WBCs/mm ³
Chest radiograph	No infiltrates	No infiltrates		
Stool examination	No RBC, few or no WBC	5 WBC/HPF with diarrhea	< 5 WBC/HPF if diarrhea	
				Caretaker contactable telephonically

Abbreviations: WBC: white blood cells; RBC: red blood cells; HPF: high power field; I:T, immature: total.

Flow chart 1 Management of fever without focus in young children
(Reproduced from Gupta P. *Textbook of Pediatrics*. New Delhi: CBS; 2013)



*Determine risk based on history, examination, and laboratory studies:

Low-risk: Normal history and physical examination; WBC 5000–15000/mm³; band cell < 1500/mm³ urine pus cells < 10/hpf; stool pus cells < 5/hpf; normal chest radiograph; and CSF < 8 lymphocytes/mm³.

[§]Other tests include WBC count; urine and stool microscopy; chest X-ray; CSF Gram stain. Cultures include that of blood, urine, and CSF.

IN A NUTSHELL

1. Children presenting with fever without localizing signs carry high chances of occult bacteremia and serious bacterial infection (SBI).
2. Newborns or young infants with fever should be hospitalized and dehydration fever ruled out, before starting empirical therapy.
3. Well appearing, 1–3 months old febrile children should be categorized into low-risk and high-risk categories, based on certain criteria.
4. Empirical antibiotic therapy should be started in children at high-risk of serious bacterial infections/occult bacteremia.

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Chapter 28.4

Fever of Unknown Origin

Bhavna Dhingra, Piyush Gupta

Fever of unknown origin (FUO) is defined as fever (rectal temperature $> 38^{\circ}\text{C}$) documented by a health-care personnel, for which no cause is identifiable after 3 weeks of outpatient evaluation and after 1 week of evaluation as an inpatient that includes a careful history and physical examination and initial laboratory assessment.

Nosocomial or health-care-associated FUO refers to hospitalized children receiving acute care in whom infection or fever were absent on admission but in whom a fever of 38°C or more occurs on several occasions, for at least a week.

Neutropenic FUO is defined as multiple readings of more than 38°C in a child with absolute neutrophil count less than $500/\text{mm}^3$, after at least 3 days of investigations including at least 48 hours of incubation of cultures.

HIV-related FUO is defined as a temperature of more than or equal to 38°C on multiple occasions for more than or equal to 3 weeks as an outpatient and more than 1 week as an inpatient in a patient with confirmed HIV infection.

Fever of unknown origin needs to be differentiated from fever without localizing signs as their differential diagnoses and most frequent causes are distinct. Children with FWLS usually need immediate evaluation and empirical antibiotic therapy, whereas those with FUO generally do not need an emergency assessment and antibiotics. The major hurdle in establishing a diagnosis is that the salient features rendering specific disorders clinically recognizable are absent or subtle. There is no *one fits all* algorithm available for evaluation and the clinician needs to work-up each case on its own merit.

ETIOLOGY

Fever of unknown origin is usually an uncommon presentation of a common illness. Infectious diseases, connective tissue diseases and autoimmune disorders are the most common causes of FUO in children. Malignancies are responsible for a lesser number of cases

as most children with malignancies present with other systemic signs or suggestive laboratory abnormalities. Drug fever, factitious fevers and periodic fever syndromes are responsible for a few cases of FUO. **Table 1** lists the common causes of FUO in children.

Epidemiologically relevant infections must be considered first in differential diagnosis and ruled out by appropriate clinical, laboratory and radiological evaluation. Hidden deep seated abscesses, e.g., pelvic, subdiaphragmatic, perinephric, subphrenic, psoas, retroperitoneal, mediastinal, dental, brain and hepatic should always be looked for and excluded. Subacute bacterial endocarditis should be high on the suspicion list especially in the setting of a pre-existing cardiac disease.

Nosocomial infections with unusual organisms, e.g., anaerobic bacilli should be considered in differential diagnosis of a patient having received various antibiotics, especially aminoglycosides, for several days in the hospital. Factitious fever should be considered, if fever persists for more than 6 months without diagnosis.

APPROACH TO DIAGNOSIS

Unless the child is acutely ill, the evaluation for FUO generally is done on an outpatient basis. If outpatient evaluation fails to disclose a cause for the fever, inpatient evaluation provides an opportunity to review the detailed history, physical examination, investigation reports and keep the child under close observation with an ongoing assessment to establish the cause of fever.

History

The history should include questions regarding characteristics of fever (onset, intensity, duration, frequency and pattern of fever). Intermittent fevers with a high spike and rapid defervescence suggest a pyogenic infection but can also be seen in tuberculosis, lymphoma, and connective tissue disorders. Remittent fevers are characterized by fluctuating peaks and a baseline that does not return to normal and are seen most commonly with viral infections, some bacterial infections (especially endocarditis), sarcoidosis, lymphoma, and atrial myxoma. Sustained fevers persist with little or no fluctuation but can appear to be intermittent if antipyretic agents are administered and are usually seen in enteric fever, typhus, brucellosis, etc. Hodgkin disease has a typical *Pel-Ebstein* type of fever (3–10 day cycles of febrile and afebrile periods). Fever with chills and rigors suggest malaria, urinary tract infection,

Table 1 Common causes of fever of unknown origin (FUO) in children

1. <i>Infections</i>
<i>Bacterial:</i> Tuberculosis, typhoid, paratyphoid, brucellosis, listeriosis, meningococcemia, yersiniosis, <i>Campylobacter</i> , relapsing fever, Lyme disease
<i>Viral:</i> Infectious mononucleosis (Epstein-Barr-virus), human immunodeficiency virus (HIV)/AIDS, hepatitis, and cytomegalovirus (CMV) disease
<i>Parasitic:</i> Malaria, kala-azar, amebic abscess, hepatic amebiasis, giardiasis, toxoplasmosis, trypanosomiasis, and visceral larva migrans
<i>Rickettsia:</i> Scrub typhus, Q fever, Rocky mountain spotted fever
<i>Fungal:</i> Disseminated candidiasis, histoplasmosis, aspergillosis, blastomycosis, disseminated coccidioidomycosis, and cryptococcosis
2. <i>Connective tissue and autoimmune disorders:</i> Systemic lupus erythematosus (SLE), juvenile idiopathic arthritis (JIA), rheumatic fever, juvenile dermatomyositis, chronic active hepatitis, polyarteritis nodosa, mixed connective tissue disorder, Behçet disease, and autoimmune thyroiditis
3. <i>Hypersensitivity disorders:</i> Drug fever, serum sickness, hypersensitivity pneumonitis, and Weber-Christian disease
4. <i>Malignancies:</i> Hodgkin disease, leukemia, lymphoma, inflammatory pseudotumors, pheochromocytoma, neuroblastoma, and Wilms tumor
5. <i>Granulomatous disorders:</i> Sarcoidosis, granulomatous hepatitis, inflammatory bowel disease
6. <i>Familial and hereditary syndromes:</i> Familial dysautonomia, familial Mediterranean fever, anhidrotic ectodermal dysplasia, Ichthyosis, and hypertriglyceridemia
7. <i>Hematologic causes:</i> Hemophagocytic lymphohistiocytosis syndromes, cyclic neutropenias, immunodeficiency states, Kikuchi-Fujimoto disease, and Castleman disease
8. <i>Endocrine causes:</i> Addison disease, thyrotoxicosis, hypothalamic central fever, and diabetes insipidus
9. <i>Miscellaneous causes:</i> Factitious fevers, infantile cortical hyperostosis, pancreatitis, drug fevers, poisonings, thrombophlebitis, and pulmonary embolism

abscesses or nosocomial infections. Relapsing fever with periods during which patients are afebrile for one or more days between febrile episodes may be seen with malaria, rat-bite fever, *Borrelia* infection, and lymphoma.

The clinician needs to enquire about the way temperature was assessed-perceived manually or documented by a thermometer along with the site of documentation; localizing symptoms of fever; recent exposures like vaccination or animal/insect bites or receipt of any blood transfusion or biological products; exposure to a family member with fever or any infectious disease, past history of any significant illnesses such as tuberculosis, urinary infections, congenital heart disease, any surgical procedure; any history of travel in the recent past to specific disease endemic areas, history of exposure to any heavy metals or poisonous fumes and history of an underlying chronic disease and medication history. History of recurrent episodes of fever may give a clue to certain cyclic causes of fever, e.g., cyclic neutropenia, and may also be seen in immunodeficiency disorders, hyperimmunoglobulin D disease and central nervous system disorders of temperature regulation. Tick bites can lead to Rocky Mountain spotted fever, ehrlichiosis, tularemia, tick-borne relapsing fever, or Lyme disease. Ingestion of raw meat or raw shellfish may lead to brucellosis, toxoplasmosis, tularemia, or hepatitis. Familial Mediterranean fever is generally seen in Jewish, Turkish, and Arab populations. Familial dysautonomia is common in Ashkenazi Jews.

Examination

A detailed clinical examination, which needs to be repeated frequently, so as not to miss any subtle or evolving signs, remains the most important clinical tool for diagnosis. While examining the child, particular attention should be paid to evaluation of skin, fundus, throat, lymph nodes, genitalia and sinuses. Detailed eye inspection including that of cornea, conjunctiva, orbit, uveal tract and retina may point towards many infectious, collagen vascular, malignant or metabolic disorders. Absence of sweating during fever may be noted in anhidrotic ectodermal dysplasia and absence of malaise or other generalized signs in a child with a history of prolonged high fevers can signal factitious fever. Careful rectal, external genitalia, and pelvic examination (where indicated) should be performed.

Laboratory Tests

The laboratory and imaging evaluations for FUO should be directed toward the likely causes of fever based upon the patient's age, duration of fever, history and findings from the physical examination. Appropriate laboratory investigations such as complete blood counts with total leukocyte count, differential leukocyte count, erythrocyte sedimentation rate (ESR), peripheral blood smear examination for malaria and filariasis (night blood) are routinely performed. **Table 2** lists the various hematological abnormalities which may be an indicator of a specific disease condition. An elevated ESR more than 30 mm/hour suggests inflammation. ESR and C reactive protein (CRP) though nonspecific, can serve as prognostic markers and be used for monitoring purposes. Simple serological tests for typhoid, brucellosis, leishmaniasis, toxoplasmosis and amebiasis, and bacteriological culture of blood for *Salmonella* and *Brucella* should be undertaken.

Repeated microscopic examination and cultures of blood, urine, throat, sputum, and stool for bacterial and fungal infections should be carried out at periodic intervals. Sterile pyuria can be a clue to Kawasaki disease or genitourinary tuberculosis. Serum electrolytes, blood urea nitrogen (BUN), creatinine, and

Table 2 Hematologic clues to specific disease states

Anemia	Malaria, Infective endocarditis, Inflammatory bowel disease, systemic lupus erythematosus, tuberculosis, etc.
Thrombocytosis	Kawasaki disease
Total white blood cell count >10,000/mm ³	Serious bacterial infection
Nonsegmented polymorphonuclear leukocytes > 500/mm ³	Serious bacterial infection
Eosinophilia	Parasitic, fungal, allergic or immunodeficiency states
Immature band forms	Leukemia
Activated lymphocytes	Viral Infection

hepatic enzymes are obtained to evaluate renal and/or hepatic involvement. Hypernatremia may be seen in diabetes insipidus, elevated hepatic enzymes may be a clue to a viral infection.

Bone marrow examination can help in diagnosing leukemia, lymphoma, histiocytic disorders, and hemophagocytic syndromes. If specifically indicated, cultures of bone marrow, cerebrospinal fluid, gastric aspirate, lymph node aspirate and liver aspirate for aerobic and anaerobic bacteria, mycobacteria and fungi may prove to be invaluable. Serum antinuclear antibody should be obtained for children with a strong family history of rheumatic disease. Serum concentrations of immunoglobulins (IgG, IgA, and IgM) should be measured in children with evidence of recurrent or persistent fever and a negative initial evaluation. Hypogammaglobulinemia may indicate an immunodeficiency, while elevated levels may be seen in chronic infections, or autoimmune disorders. Serological tests should also be repeated to look for any rising antibody titers. Modern molecular diagnostic techniques; e.g., polymerase chain reaction (PCR) are now available for diagnosis of several infectious agents. A variety of immunological tests for detection of various autoantibodies is now available to rule out various autoimmune disorders.

Diagnostic imaging of the nasal sinuses, mastoids, chest and gastrointestinal (GI) tract by radiography, barium studies, ultrasonography, computerized tomographic (CT) scans and magnetic resonance imaging (MRI) as indicated, should initially be performed for specific indications, but may be done in children in whom FUO persists without a cause being established. Endoscopic evaluation of respiratory, genitourinary and gastrointestinal tract may help positron emission tomography (PET) scanning and immunoscintigraphy may be helpful in patients with persistent FUO who remain without a diagnosis after initial evaluation. Lymphangiography can be resorted to, for demonstrating retroperitoneal, iliac and periaortic lymph nodes. Biopsy (e.g., of lymph nodes, bone marrow or liver) should be reserved only for children with evidence of involvement of specific organs. If indicated, skin, pleura, muscle, kidneys, etc. can also be biopsied.

MANAGEMENT

Empirical treatment with anti-inflammatory agents (except for symptomatic relief in suspected JIA) or antibiotics should be avoided as they may mask the diagnosis or alter the course of certain conditions like infective endocarditis, meningitis or osteomyelitis and may also interfere with isolation of certain microorganisms on cultures. Disease specific appropriate interventions should be initiated soon after establishing the diagnosis.

IN A NUTSHELL

1. Fever of unknown origin (FUO) is defined as fever (rectal temperature $> 38^{\circ}\text{C}$) documented by a health-care personnel, for which no cause is identifiable after 3 weeks of outpatient evaluation and after 1 week of evaluation as an inpatient.
2. A detailed clinical history and examination, repeated frequently, is crucial for diagnosis of FUO.
3. Infectious diseases, connective tissue diseases and autoimmune disorders are the most common causes of FUO in children.
4. Children with FUO generally do not need an emergency assessment or empirical anti-inflammatory agents and/or antibiotics.

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Section 29 BACTERIAL INFECTIONS

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Chapter 29.1

Natural History of Bacterial Infection

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KOCH'S POSTULATES

It may not be very easy to show that a specific bacterial species is the cause of a particular disease. Robert Koch (1884) proposed a set of postulates, which are applied broadly to link specific bacterial species with specific diseases (**Box 1**).

BOX 1 Koch's postulates

- The microbial pathogen should be present in all cases of the disease in question, and its distribution should be in accordance with the lesions observed in the body
- The microorganism should be grown in pure culture *in vitro* or outside the body of the host for several generations
- When a pure culture of the microorganism is inoculated into susceptible animal species, the typical disease must result
- The microorganism must again be isolated from the lesions of such experimentally produced disease.

Koch's postulates permit the bacteria to be classified as pathogens, opportunistic pathogens or nonpathogens. Some bacterial species are always considered to be pathogens and their presence is abnormal, e.g., *Mycobacterium tuberculosis* and *Yersinia pestis*. These bacteria readily fulfill Koch's postulates. Some bacterial species are part of the normal flora of humans and animals but may also frequently cause disease—*E. coli* is a part of the gut flora in humans, but it is also a common cause for urinary tract infections. Other bacteria only cause disease in immunosuppressed or immunocompromised persons and are *opportunistic pathogens* (e.g., *Pseudomonas*).

However, there are many pathogenic microorganisms which fail to meet one or the other criteria of these postulates. Agents of syphilis (*Treponema pallidum*) and leprosy (*Mycobacterium leprae*) have not been grown *in vitro*; but there are animal models of infection with these agents. The agent of gonorrhea (*Neisseria gonorrhoeae*) is readily cultivable in the laboratory though there is no animal model of infection. Nonetheless, experimental infection in humans has been produced which substitutes for an animal model.

TRANSMISSION OF INFECTION

Some bacteria that commonly cause human disease primarily exist in animals and incidentally infect humans, e.g., *Salmonella* species infect animals and are transmitted to humans through meat and meat products. Certain bacteria do not involve humans in their normal life cycle, and, therefore, they are not adapted to

the human body. This results in the outbreak of a severe form of the disease. *Yersinia pestis*, the agent of plague has an established life cycle in rodent and rodent fleas, and its transmission by the fleas to humans is inadvertent. The *Clostridium* species are ubiquitous in the soil and are transmitted to humans by ingestion (*C. perfringens* gastroenteritis and *C. botulinum* food-poisoning) or by contamination of wounds with soil (*C. perfringens* gas gangrene and *C. tetani* tetanus).

The symptoms of diseases (i.e., rhinorrhea, diarrhea, genital discharge) caused by microorganisms often promote transmission of the agents. *Vibrio cholerae* can cause copious diarrhea, which may contaminate river or drinking water. Ingestion of these can subsequently result in infection and disease.

THE INFECTIOUS PROCESS

The bacteria lodge themselves in or on a host, and set about establishing a primary site of infection. Subsequently, they multiply and spread through tissues or lymphatic system to the bloodstream, leading to bacteremia, which can be transient or persistent. Hematogenous route disseminates bacteria widely in the body and transports them selectively to tissues suitable for their growth.

Streptococcus pneumoniae are normally present in the nasopharynx of 5–40% of the healthy population. Occasionally these may get aspirated into the lungs and cause infection in the terminal air spaces of the lungs. Multiplication of the pneumococci and resultant inflammation lead to pneumonia. The pneumococci enter the lymphatics of the lungs and move to the bloodstream. Bacteremia is present in only 10–20% of persons with pneumococcal pneumonia. Following bacteremia, pneumococci can spread to secondary sites of infections, e.g., cerebrospinal fluid, joint spaces and heart valves resulting in meningitis, septic arthritis and endocarditis, respectively.

The infectious process in cholera involves ingestion of *V. cholerae* (VC), chemotactic attraction of the bacteria to the gut epithelium, motility of the bacteria by a single polar flagellum, and penetration of the mucus layer on the intestinal surface. The *V. cholerae*'s adherence to the epithelial cell surface is mediated by pili. The cholera toxin produced leads to the inflow of chloride and water into the lumen of the gut causing diarrhea and electrolyte imbalance.

BACTERIAL VIRULENCE FACTORS

Many factors determine the bacterial virulence or ability to cause infection and disease. These include the adherence factors, ability to invade the host and produce toxin, and presence of various tissue-degrading enzymes, peptidoglycans, IgA proteases, anti-phagocytic factors, intracellular pathogenicity and antigenic heterogeneity. Some of these factors are discussed below:

Adherence factors Once bacteria enter the body of the host, they must adhere to cells of a tissue surface; otherwise they would be swept away by mucus and other body fluids. The interactions between bacteria and tissue cell surface in the adhesion process

are complex, and several factors are involved. Bacteria and the host cell commonly have negative surface charges, i.e., repulsive electrostatic forces, which are overcome by hydrophobic interaction between the two cells. The more hydrophobic the bacterial cell surface, the greater is the adherence to the host cells; different strains of bacteria within a species may vary widely in their hydrophobic capability.

Bacteria also have specific surface molecules that interact with host cells. Pili are hair-like appendages that extend from the bacterial cell surfaces. The *E. coli* that cause diarrhea have pili mediating adherence to intestinal epithelial cells. Group A streptococci and *Streptococcus pneumoniae* also have hair-like appendages termed fibrillae, that extend from their cell surfaces. The cell wall's lipoteichoic acid causes adherence of the streptococci to buccal epithelial cells; M-protein acts as an antiphagocytic molecule. Certain bacteria employ other specific ligand-receptor mechanisms to promote bacterial adherence to host cells.

Invasion of host cells and tissues Invasion is the term commonly used to describe the entry of bacteria into the host cells, implying an active role for the organisms and a passive role for the host cells. In many infections, the bacteria produce virulence factors that influence the host cell, causing them to engulf the bacteria. The host cells also play a very active role in this process.

Invasion of the host epithelium is central to the infectious process of some bacteria, e.g., *Salmonella*, *Yersinia* and *Chlamydiae*. Once inside the host cell, bacteria may remain enclosed in a vacuole or be dispersed in the cytoplasm. Some bacteria such as shigellae multiply within the host cells.

Shigella species adhere to host cells in vitro. The adherence induces the formation of pseudopods by the host cells, which engulf the bacteria. At least three proteins (invasion plasmid antigens: Ipa—Ipa B, Ipa C and Ipa D) contribute to the process. Once inside the host cells, the shigellae are either released or escape from the phagocytic vesicle and multiply in the cytoplasm. The pathogenesis of *Shigella* adherence and invasion in vivo appears to be different. After adhering to the surface of M-cells in Peyer's patches, shigellae are phagocytosed and escape killing by the macrophages. Further spread to adjacent cells occurs in a similar manner.

Neisseria gonorrhoeae use pili as primary adhesins and opacity associated protein (Opa) as secondary adhesins to enter host cells. Certain Opa proteins mediate adherence to polymorphonuclear cells. Some gonococci survive after phagocytosis by these cells. Pili and Opa together enhance the invasion of cells cultured in vitro. Further intracellular multiplication and migration to sub-epithelial space occurs by an unknown mechanism.

TOXINS

Toxin production and other virulence properties are generally independent of the ability of the bacteria to invade cells and tissues. Toxins are generally classified into two groups: endotoxins and exotoxins.

Endotoxins

These are integral parts of the cell wall of *gram-negative* bacteria and are released on bacterial death and in part during their growth. They do not necessarily need to be released to have biological activity. Endotoxins are stable lipopolysaccharide complexes and can withstand temperatures above 60°C for hours without loss of toxicity. These are weakly antigenic and may produce protective antitoxic antibodies. However, protective relationship between antibody titers and protection from disease is less clear than with exotoxins.

Endotoxins are moderately toxic and very high doses are fatal. These cannot be converted into toxoids. They usually produce fever

in the host by the release of interleukin-1 and other mediators. Some of the clinical conditions where endotoxins are implicated include septic shock, fulminant hepatic failure, cirrhosis, obstructive jaundice, inflammatory bowel disease, acute renal failure, acute respiratory distress syndrome, major abdominal trauma, neonatal necrotizing enterocolitis, radiation injury, graft versus host disease and toxic shock syndrome. Endotoxins in the bloodstream are initially bound to circulating proteins, which then interact with receptors on macrophages and monocytes and other cells of the reticuloendothelial system. Interleukin-1, tumor necrosis factor and other cytokines are released and the complement and coagulation cascades are activated. This results in fever, leucopenia, hypotension and shock due to impaired perfusion of essential organs such as brain, kidney and heart. The end result is massive organ dysfunction and death.

Exotoxins

Exotoxins are produced by both, living *gram-positive* and *gram-negative* bacteria. These are relatively unstable polypeptides and their toxicity gets rapidly destroyed at temperatures above 60°C. They are highly immunogenic and stimulate formation of high titer antitoxin. Antitoxin can completely neutralize toxin. Exotoxins, though highly toxic, can be converted to antigenic nontoxic *toxoids* by heat and formalin. They are used for immunization purposes (e.g., diphtheria toxoid). Release of exotoxin in the host usually does not produce fever.

Some of these toxins have had major roles in world history—tetanus caused by the exotoxin of *Clostridium tetani* killed as many as 50,000 soldiers during the Second World War. Vaccines called toxoids have been developed for some of the exotoxin mediated diseases, and continue to be important in the prevention of disease. Many exotoxins consist of A and B subunits. The A subunit provides the toxin activity and the B subunit generally mediates adherence of the toxin complex to the host cell and aids its entry into it. Cited below are few examples of exotoxins and their effects.

C. diphtheriae It is a gram-positive bacillus which produces diphtheria toxin causing diphtheria. It affects the heart, kidney, liver and adrenals and can be lethal in a dose of 0.1 mg/kg.

Clostridium tetani It is an anaerobic gram-positive bacillus that causes tetanus. This bacillus, present in the environment, contaminates the wound, and its spores germinate in the anaerobic environment of the devitalized tissue; infection often is minor and not clinically apparent. The vegetative forms of *Clostridium tetani* produce the toxin *tetanospasmin*, which has two peptides (Mr 50,000 + Mr 1,00,000)—the larger peptide binds to gangliosides, the smaller peptides appear to have toxic activity. Tetanospasmin reaches the central nervous system by retrograde transport along axons and through the systemic circulation. It blocks the release of an inhibitory mediator in the nerve endings resulting in generalized muscle spasms. Extremely small amount can be lethal for humans. Tetanus is totally preventable in immunologically normal people by immunization with tetanus toxoid.

Clostridium botulinum (CB) It causes botulism. CB is found in soil or water and may grow in canned vacuum packed foods. It produces the most potent toxin known on earth; it is heat labile. The toxin is absorbed from the gut and carried to motor nerves where it blocks the release of acetylcholine at the neuromuscular junctions resulting in flaccid paralysis.

Clostridium perfringens (*syn C. Welchii*) It causes gas gangrene. Its spores enter the wound when contaminated with soil or feces. In the presence of necrotic tissue, they germinate and produce several histiocytic and membrane damaging toxins. Many of these are lethal, cytolytic and necrotizing, and favor the spread of gas gangrene.

Staphylococcus aureus (SA) It grows on mucous membranes or in wounds and may liberate toxin-1 (TSST-1) which causes toxic shock syndrome (TSS). The illness is characterized by shock, high fever, a diffuse red rash that later desquamates with multiple system involvement. Toxic shock syndrome also occurs during immunization sessions where measles vaccines are contaminated with SA. *S. aureus* also produces an epidermolytic toxin that acts on stratum granulosum of the epidermis and results in scalded skin syndrome. Other toxins liberated are α , β , γ , δ , hemolytic toxins— α toxin has a cytotoxic role and is responsible for wound infections and septicemia.

Enterotoxins

Exotoxins associated with diarrheal illnesses and food poisoning are called enterotoxins. A list of these toxins and their mode of action along with the diseases produced by them is given in **Table 1**.

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Table 1 Bacterial toxins that affect the intestine (enterotoxins)

Organism	Disease	Toxin	Mode of action
<i>Vibrio cholerae</i>	Cholera	Cholera toxin	Activation of adenylate cyclase and elevation of intracellular AMP
<i>Shigella dysenteriae</i>	Dysentery	Shiga toxin	Enterotoxic, cytotoxic and neurotoxic inhibits protein synthesis
Enteropathogenic <i>E. coli</i> (EPEC)	Diarrhea	Low levels of shiga like toxin, (SLT-1 and SLT-2)	Enterotoxic, cytotoxic, neurotoxic antigenically related but not identical to Shiga toxin
Enteroinvasive <i>E. coli</i> (EIEC)	Dysentery like illness	Multiple SLTs	
Enterohemorrhagic <i>E. coli</i> (EHEC)	Hemorrhagic colitis, hemolytic uremic syndrome, voluminous diarrhea	High level of SLT	
Enterotoxigenic <i>E. coli</i> (ETEC)	Diarrhea	Heat-labile toxin Heat-stable toxin	Related to cholera toxin, activates adenylate cyclase Short peptide, nonantigenic, activate particulate fraction of guanylate cyclase leading to elevation of cyclic GMP
<i>Bacillus cereus</i>	Food-poisoning with vomiting and diarrhea	Diarrheagenic toxin/lethal toxin	Precise basis of toxin action at cellular level not known, causes fluid accumulation, increased vascular permeability and necrosis
<i>Staphylococcus aureus</i>	Food-poisoning with vomiting	Seven types of enterotoxin, A, B, C1, C2, C3, D, E	Molecular basis not known, causes fluid imbalance in colon. Believed to stimulate vomiting center through vagus nerve. Also causes systemic effects
<i>Clostridium difficile</i>	Pseudomembranous colitis	Toxin A	Enterotoxic, lethal; causes fluid accumulation and hemolytic diarrhea
<i>Clostridium perfringens</i>	Food-poisoning with diarrhea	Toxin B Cytotoxic, enterotoxin	Lethal, acts intracellularly Cytotoxic damage to intestinal epithelial cells

Chapter 29.2

Principles of Antibiotic Therapy

Anita Shet

Antimicrobial agents include some of the most widely used therapeutic agents worldwide. The terms antibiotic, antimicrobial and anti-infective agents are often used interchangeably, and encompass a wide variety of pharmaceutical agents that include antibacterial, antifungal, antiviral and antiparasitic drugs. Among these agents, antibacterial agents are the most common, and are a focus of this chapter. A child, who develops features suggestive of an infection, requires a physician who must first determine whether the infection is likely to be caused by an organism that is susceptible to antimicrobial therapy. The selection of optimal antibiotic therapy for the child is based on the assessment of need, benefits, costs and risk of the specific therapy for each child. Inappropriate selection of antibiotic therapy subjects the child to unnecessary toxicities, possible risk of drug-resistant bacterial infection, erroneous diagnosis and needless costs to the individual and to the society.

Evidence-based guidelines are available and can be used for many situations that call for targeted therapy for specific infectious diseases where the specific microorganisms are known or assumed. However, these guidelines should be applied in the context of host characteristics, cost and availability of therapy, and response to therapy. This chapter presents general principles that guide appropriate use of antibiotic therapy that benefit the individual child and family as well as society.

SELECTION OF AN OPTIMAL ANTIBIOTIC REGIMEN

There are several steps toward selecting an optimal antibiotic regimen. These steps must be sequentially addressed in order to select the best possible therapy that will bring the maximum benefit to the child.

1. Predicting the Pathogen

The first step in selecting a suitable antibiotic is establishing the infectious disease diagnosis. One needs to define the site of infection and the host status. Knowledge that certain species of bacteria have a predilection for certain tissues is essential. For example, *Neisseria meningitidis*, group B streptococci and *Streptococcus pneumoniae* are likely to infect the central nervous system and cause meningitis, while *Staphylococcus aureus* and *Streptococcus pyogenes* have a proclivity for skin and bone infections. One may also eliminate certain pathogens based on the site of infection; for instance, in uncomplicated urinary tract infections, *Staphylococcus aureus* may be dismissed as a likely pathogen.

2. Considering Age of the Child

The age of the child can often predict the bacterial pathogen; group A *Streptococcus*, *Listeria monocytogenes* and *Escherichia coli* are the most likely pathogens in meningitis in infants in the first 3 months of age, while *Streptococcus pyogenes* from school-related exposure is more common in older children. *Staphylococcus aureus* as a cause for severe pneumonia is more likely to be thought of in preschool children rather than those above 6 years of age.

3. Factoring in Host Status

Infecting pathogens are predictable if the child is healthy, has intact immunity and normal barriers to infection. If the child has

an underlying T-cell or B-cell lymphocyte defect, bacteria that are not normally pathogenic can also cause infection. In predicting possible pathogens, host factors that need to be considered include trauma to skin or mucous membranes, presence of a foreign body, a recent surgical procedure, an indwelling medical device or presence of immunosuppressive agents.

4. Ascertaining a Medical and Microbiological Diagnosis

Maximum efforts should be made to arrive at a diagnosis of the infectious disease syndrome, derive the etiology of the infection, and obtain a microbiological isolate for accurate diagnosis and susceptibility testing. The power of the Gram stain (and other appropriate stains) along with simple microscopy should never be underestimated. In addition, bacterial cultures and susceptibility tests should be obtained whenever possible. Rapid diagnostic tests, such as latex agglutination tests for *Streptococcus pneumoniae*, also have a place in diagnosis, although the sensitivity and specificity of these tests may need improvement. Molecular techniques are emerging as diagnostic modalities, which, when done meticulously, have a useful place in the diagnosis of the infection and appropriate antibiotic selection.

5. Testing Antibiotic Susceptibilities

There may be wide variation in the antibiotic susceptibility patterns in different areas, even when the organisms are similar. For instance, in a single geographic area, it is possible that an *E. coli* isolate from a urinary tract infection in a child previously unexposed to antibiotics will have a different susceptibility pattern from an *E. coli* isolate from a child undergoing several chemotherapy cycles for leukemia, and versus a similar isolate from preterm infant in an intensive care unit. Geographic variations may also be due to differing patterns of antibiotic use in these areas. A hospital antibiogram is a useful tool in selecting antibiotics for different infections, as the susceptibility patterns reflect the local trends prevailing in that region. The probability that the selected antibiotic will be effective against the presumed bacterial pathogen is directly related to the proportion of infected pathogens infecting patients in that location. The susceptibility of a specific bacterial pathogen to an antimicrobial agent can be measured in the laboratory by defining the lowest concentration of the antibiotic that can inhibit the growth of the pathogen, the minimum inhibitory concentration (MIC), measured in µg/mL.

6. Considering Specific Properties of the Antibiotic

The selection of the antimicrobial agent is guided by specific properties of the drug, particularly the administration route, absorption, the tissue distribution of the antibiotic at the site of infection, and drug elimination characteristics.

Pharmacodynamics

Understanding pharmacodynamics of antimicrobials is important in predicting microbiologic and clinical success of antibiotic treatment. The antibiotic effect is related directly to either the concentration attained at the site of infection or the time during which an effective concentration of the antibiotic is present at the site of infection. Aminoglycosides and fluoroquinolones exhibit *concentration-dependent killing* indicating that higher concentrations of the drug result in more rapid killing. These antibiotics also exhibit a prolonged antibiotic effect even after the serum level decreases below the MIC for the particular organism. Thus, higher doses and often once-daily doses result in greater efficacy.

Beta-lactam antibiotics, erythromycin, clindamycin, vancomycin and linezolid demonstrate *time-dependent killing*, where

optimal activity is related to the time during which the antibiotic concentration remains above the MIC at the site of infection. For these antibiotics, having greater antibiotic concentrations at the site of infection would not achieve a greater inhibitory effect. These agents also exhibit a postantibiotic effect, where bacterial growth is inhibited for a substantial time after exposure to the antibiotic.

Pharmacokinetics

Pharmacokinetics includes the absorption, concentration, distribution, metabolism and excretion of the antibiotic, and these parameters can vary widely in children based on age, other host factors and illness severity. The volume of distribution of antibiotics varies profoundly during the first few years of life, and is greater in the neonate compared to the infant. Drug elimination is low at birth, peaks in infancy and then reaches adult values gradually in later childhood. Thus, the dose of antibiotics needs adjustment during different ages, in order to maintain efficacy and minimize toxicity.

Specific concentrations of antibiotics may vary in tissues and organs, and different body compartments can have widely differing antibiotic elimination half-lives. The route of administration plays a role in optimal efficacy. In general, most parenteral antibiotics result in higher serum concentrations than when given orally. Selecting the most appropriate antibiotic dose, when switching from intravenous to oral therapy, depends most on the absorption characteristics of the oral agent. Oral bioavailability is fair for most beta-lactam antibiotics; serum concentrations are only 5–10% of those obtained when beta-lactam antibiotics are given parenterally. On the other hand, quinolones have excellent bioavailability; serum concentrations after an oral dose are close to that found after an intravenous dose.

7. Selecting Empiric vs. Definitive Antimicrobial Therapy

When an infection is identified, empiric therapy is instituted based on the presumed pathogen, local resistance patterns and the risk of severity of the infection. In general, with increasing severity of infection in the child, the need to start antibiotics with appropriately broad antibacterial activity at the highest tolerated dose as empiric therapy becomes increasingly urgent.

Broad-spectrum Therapy

In critically ill patients, broad-spectrum antibiotics such as beta-lactam/beta-lactamase inhibitor combinations such as co-amoxiclavulanic acid and piperacillin-tazobactam, third generation cephalosporins, quinolones, and carbapenems, are useful for initial empiric therapy. These antibiotics cover a greater range of pathogens and should be switched to more targeted therapy once the offending pathogen has been identified. Prolonged or extensive use of broad-spectrum agents can lead to selection of drug resistant bacteria, fungal infections and antibiotic-associated diarrhea.

Narrow-spectrum Therapy

Whenever possible, it is preferable to use narrow spectrum agents such as penicillin, trimethoprim, erythromycin and cloxacillin. Once the pathogen is identified, a narrow-spectrum agent can provide the same degree of bacterial eradication and clinical efficacy with decreased toxicity, decreased drug resistance risk and decreased costs. An example is the treatment of ventilator-associated pneumonia; initial empiric treatment with a carbapenem agent can be narrowed to more targeted therapy with cefotaxime if susceptible *Klebsiella* species is isolated.

8. Considering Antibiotic Efficacy at the Site of the Infection

The capacity of the selected antibiotics to achieve a concentration equal to or greater than the MIC at the site of infection plays a critical role in maintaining the efficacy of the regimen. At certain body compartments, such as cerebrospinal fluid, bone, middle ear compartment and abscess cavities, the antimicrobial concentration achieved may be several times lower than the serum level of the antimicrobial agent. Examples include macrolides and first- and second-generation cephalosporins that do not cross the blood-brain barrier, and hence are not recommended for central nervous system infections. Aminoglycosides are less active in the acidic, low-oxygen milieu of abscess cavities, and hence are less efficacious antimicrobial agents in such settings, unless there is complete drainage of the abscess. Variations within the same class of antibiotics also exist; moxifloxacin achieves poor concentration in the urine due to its low renal excretion, while ciprofloxacin achieves good concentrations and works well against urinary infections caused by susceptible bacteria. Clindamycin and fluoroquinolones achieve good tissue concentrations in bone and are excellent agents for bone and joint infections.

9. Deciding the Duration of Antibiotic Therapy

Factors that determine the optimal duration of therapy depend on the severity of the infection, virulence of the infecting pathogen, susceptibility to the antimicrobial agent used, penetration of the antibiotic at the site of infection, and host factors that may impair antimicrobial activity. Longer treatment courses may be recommended for resistant organisms or immunocompromised hosts. For most infections, a recommendation for duration of therapy is based on the best available evidence for that particular childhood infection, together with experience and consensus. For example, the recommended duration of treatment in childhood meningitis varies according to the infecting organism as follows: *Neisseria meningitidis*, (5–7 days); *Streptococcus pneumoniae* (10–14 days); Gram-negative enteric bacilli (21 days).

10. Therapeutic Drug Monitoring

The therapeutic index of an antibiotic is the ratio of its toxic dose to its therapeutic dose. Most antimicrobial agents have a wide therapeutic index, and allow standard doses to be used, except when adjustments have to be made for age, renal or hepatic function. Some antibiotics such as aminoglycosides and vancomycin that demonstrate toxicity at high doses require monitoring of serum levels due to their narrow therapeutic index.

Table 1 provides a classification of antibiotics, resistance mechanisms and spectrum of activity. Reasons why a particularly prescribed antibiotic does not work are listed in **Box 1**.

BOX 1 Why is my antibiotic not working?

- Incorrect dose of antibiotic
- Incorrect choice of antibiotic
- Wrong organism—viruses
- Not reaching site of infection (deep abscess)
- Defective immune system
- Drug fever.

ANTIMICROBIAL PROPHYLAXIS

Appropriate prophylactic antimicrobial use in a patient is governed by the following principles; a high risk of infection is present in the patient, the degree and duration of risk can be estimated, and the likely offending organisms and their susceptibility patterns are known. Prophylaxis may be short- or long-term.

Table 1 Classification of antibiotics, resistance mechanisms and spectrum of activity

Antibiotic class	Antibiotic examples	Spectrum of activity	Mechanism of resistance
Beta-lactam antibiotics			
Natural penicillins	Benzyl penicillin, Penicillin V	Gram-positive: Streptococci, pneumococci, <i>Enterococcus</i> species Gram-negative: <i>Neisseria</i> species, <i>Treponema pallidum</i> , <i>Leptospira</i> species Anaerobes	• Beta-lactamase production, including extended-spectrum beta-lactamase (ESBL) and carbapenemase
Semisynthetic penicillin	Cloxacillin	Gram-positive: As above, and <i>Staphylococcus aureus</i> (except MRSA)	• Altered penicillin-binding proteins
Aminobenzyl penicillin	Ampicillin, Amoxicillin	Gram-positive: As above Gram-negative: <i>E. coli</i> , <i>H. influenzae</i> , <i>Neisseria</i> species	
Ureidopenicillin	Piperacillin	Gram-positive: As above Extended Gram-negative coverage: <i>Proteus</i> , <i>Pseudomonas</i> , <i>Enterobacter</i> species	
Beta-lactase inhibitor combinations	Ampicillin/sulbactam, Amoxicillin/clavulanate, Piperacillin/tazobactam	Gram-positive: As above. <i>Staphylococcus aureus</i> (except MRSA), beta-lactamase producing strains. Extended Gram-negative and anaerobic coverage	
Cephalosporins			
First generation	Cefazolin, Cefalexin, Cefadroxil	Gram-positive: Streptococci, Pneumococci, <i>Enterococcus</i> species <i>Staphylococcus aureus</i> (except MRSA) Gram-negative: <i>E. coli</i>	
Second generation	Cefuroxime, Cefaclor, Cefoxitin, Cefotetan	Gram-positive: As above Gram-negative: Including enterobacteriaceae (<i>E. coli</i> , <i>Klebsiella</i> , <i>Proteus</i> , <i>Salmonella</i> , <i>Shigella</i> , etc.) Some anaerobes	
Third generation	Cefotaxime, Ceftriaxone, Ceftazidime, Cefixime, Cefpodoxime, Cefoperazone	Gram-positive: As above Extended Gram-negative: <i>Pseudomonas</i> , <i>Serratia</i> species Anaerobes	
Fourth generation	Cefepime	As above, including <i>Pseudomonas aeruginosa</i>	
Carbapenems			
	Imipenem, Meropenem, Ertapenem	Gram-positive: As with third generation cephalosporins above Extended Gram-negative: <i>Pseudomonas</i> , <i>Serratia</i> species Anaerobes	
Monobactams			
	Aztreonam	Gram-negative: <i>Citrobacter</i> , <i>Enterobacter</i> , <i>E. coli</i> , <i>Klebsiella</i> , <i>Pseudomonas</i> species	
Aminoglycosides			
	Streptomycin, Gentamicin, Amikacin	Gram-positive: <i>Staphylococcus aureus</i> (rare) Gram-negative: <i>E. coli</i> , <i>Klebsiella</i> , <i>Enterobacter</i> , <i>Serratia</i> , <i>Proteus</i> , <i>Citrobacter</i> , <i>Acinetobacter</i> , <i>Pseudomonas</i> species	• Enzymatic inactivation • Altered uptake • Efflux pump
Tetracyclines			
	Doxycycline, Minocycline	Gram-positive: <i>Actinomyces</i> species Gram-negative: <i>Vibrio cholerae</i> , <i>Brucella</i> , <i>Campylobacter</i> , <i>Yersinia</i> , <i>Neisseria</i> species Others: <i>Borrelia</i> , <i>Neisseria</i> species, <i>T. pallidum</i>	• Efflux pump
Glycylcyclines			
	Tigecycline	Gram-positive: Streptococci, Enterococci species (including vancomycin resistant species, <i>Staphylococcus aureus</i> (including MRSA)). Gram-negative: <i>Acinetobacter</i> , <i>Aeromonas</i> , <i>Citrobacter</i> , <i>Enterobacter</i> , <i>Klebsiella</i> , <i>Serratia</i> species Others: <i>Chlamydia</i> , <i>Mycoplasma</i> species	• Efflux pump
Quinolones			
	Norfloxacin	Gram-negative coverage	• Altered binding • Efflux pump
	Ciprofloxacin	Gram-positive: <i>Staphylococcus aureus</i> , streptococci species Gram-negative: <i>Aeromonas</i> , <i>Acinetobacter</i> , <i>E. coli</i> , <i>Klebsiella</i> , <i>Enterobacter</i> , <i>Citrobacter</i> , <i>Campylobacter</i> , <i>Proteus</i> , <i>Shigella</i> , <i>Salmonella</i> , <i>Pseudomonas</i> species.	
	Levofloxacin, Moxifloxacin	Gram-positive and negative: As above Anaerobes: <i>Clostridium perfringens</i> Others: <i>Mycoplasma</i> , <i>Legionella</i> species	

Contd...

Antibiotic class	Antibiotic examples	Spectrum of activity	Mechanism of resistance
Lincosamides	Clindamycin	Gram-positive: Streptococci, Pneumococci, <i>Staphylococcus aureus</i> Anaerobes: <i>Bacteroides fragilis</i> , <i>Prevotella</i> , <i>Fusobacterium</i> , <i>Peptococcus</i> , <i>Peptostreptococcus</i> , <i>Propionibacterium</i> species	<ul style="list-style-type: none"> Altered binding due to ribosomal modification Efflux pump Drug inactivation
Sulfonamides/trimethoprim	Cotrimoxazole	Gram-positive: <i>Streptococcus pneumoniae</i> Gram-negative: <i>E. coli</i> , <i>Klebsiella</i> , <i>H. influenzae</i> Others: <i>Pneumocystis jirovecii</i>	<ul style="list-style-type: none"> Overproduction of target dihydrofolate reductase Altered binding
Nitroimidazoles	Metronidazole	Anaerobes: <i>Clostridium</i> species, <i>Fusobacterium</i> , <i>Bacteroides fragilis</i> , <i>Peptococcus</i> , <i>Peptostreptococcus</i>	<ul style="list-style-type: none"> Inactivating enzyme
Glycopeptide	Vancomycin, Teicoplanin, Telavancin	Gram-positive: Streptococci, Enterococci, <i>Staphylococcus aureus</i> , including MRSA, <i>Staphylococcus epidermidis</i> , <i>Actinomyces</i> species Anaerobes: <i>C. difficile</i>	<ul style="list-style-type: none"> Altered binding Overproduction of target
Macrolide	Erythromycin, Azithromycin	Gram-positive: <i>Corynebacterium</i> species, <i>Listeria</i> , <i>Staphylococcus aureus</i> , <i>Streptococcus pneumoniae</i> , <i>Streptococcus pyogenes</i> Gram-negative: <i>Bordetella pertussis</i> , <i>Neisseria gonorrhea</i> Others: <i>Chlamydia trachomatis</i> , <i>Mycoplasma</i> species, <i>Ureaplasma urealyticum</i>	<ul style="list-style-type: none"> Altered binding Efflux pump
Streptogramins	Quinupristin/dalfopristin	Gram-positive: <i>Streptococcus</i> group A, B, <i>Staphylococcus aureus</i> , <i>Enterococcus faecium</i>	<ul style="list-style-type: none"> Enzymatic modification Altered target site Efflux ATP-binding pump
Oxazolidinones	Linezolid	Gram-positive: <i>Streptococcus</i> group A, B, <i>viridans</i> streptococci, <i>Staphylococcus aureus</i> , <i>Enterococcus faecium</i> , <i>Enterococcus faecium</i> , <i>Enterococcus faecalis</i>	<ul style="list-style-type: none"> Altered binding
Ketolides	Telithromycin	Gram-positive: <i>Staphylococcus aureus</i> , <i>Streptococcus pneumoniae</i> , <i>Streptococcus pyogenes</i> Gram-negative: <i>H. influenzae</i> , <i>Moraxella catarrhalis</i> Others: <i>Chlamydia trachomatis</i> , <i>Mycoplasma</i> species, <i>Ureaplasma urealyticum</i>	<ul style="list-style-type: none"> Altered binding due to modification of the ribosomal drug-binding site Efflux pump
Lipopeptides	Daptomycin	Gram-positive: <i>Staphylococcus aureus</i> (including MRSA), streptococci, <i>viridans</i> streptococcus, enterococci species	<ul style="list-style-type: none"> Altered membrane potential, causing reduced binding of drug to target site
Polymyxins	Colistin, Polymyxin B	Gram-negative: <i>Enterobacteriaceae</i> , ESBL-producing	<ul style="list-style-type: none"> Altered binding
Ansamycins	Rifampicin	Gram-positive: <i>Staphylococcus aureus</i> Gram-negative: <i>Neisseria meningitidis</i> , <i>H. influenzae</i> Other: <i>Mycobacterium tuberculosis</i>	<ul style="list-style-type: none"> Altered binding

Short-term prophylaxis A short course of antibiotics may be taken by close contacts of an ill patient in order to prevent transmission of the infection. For example, in bacterial meningitis, close contacts of the patient are advised a two-day course of rifampicin prophylaxis.

Long-term prophylaxis A postsplenectomy patient, who is under five years of age, should be advised to take penicillin twice daily, until completion of five years of age or for two years, whichever is later. Children with recurrent urinary tract infections, often as a result of anatomical abnormalities, such as vesicoureteral reflux, are prescribed long-term antibiotic prophylaxis with trimethoprim-sulfamethoxazole, nitrofurantoin or penicillins.

Surgical prophylaxis Antibiotics may be used to prevent infection during surgery. The appropriate antibiotic should be active against the pathogens most likely to contaminate the surgical site, and should be administered for the shortest effective period to minimize adverse effects, costs and drug resistance development. The type of surgery plays a crucial role in deciding about surgical prophylaxis. In many *clean* surgical procedures that are not associated with opening body cavities or inflamed tissue, such as simple facial surgery, antimicrobial prophylaxis is not indicated. On the other

hand, in *clean-contaminated* procedures that involve the opening of body cavities, or for *contaminated* procedures involving acute inflammation or visible wound contamination, antimicrobial prophylaxis is definitely indicated. For example, for percutaneous endoscopic gastrostomy (PEG) insertion, a single dose of first generation cephalosporin such as cefazolin, or alternatively, clindamycin is recommended. Similarly, for neurosurgical craniotomy or ventriculoperitoneal shunting procedures, a single dose of cefazolin or clindamycin is recommended.

Sites of action for major antibiotics are given in **Figure 1**.

ANTIMICROBIAL COMBINATIONS

Improved anti-infective efficacy is often achieved with combination of other drugs or antimicrobials. Clinical benefit of combination therapy may be achieved in the following ways:

Prevention of Emergence of Resistance

In the treatment of *Mycobacterium tuberculosis* infections, the use of two or more active agents can reduce the probability of resistant organisms developing. In invasive pseudomonal infections, the

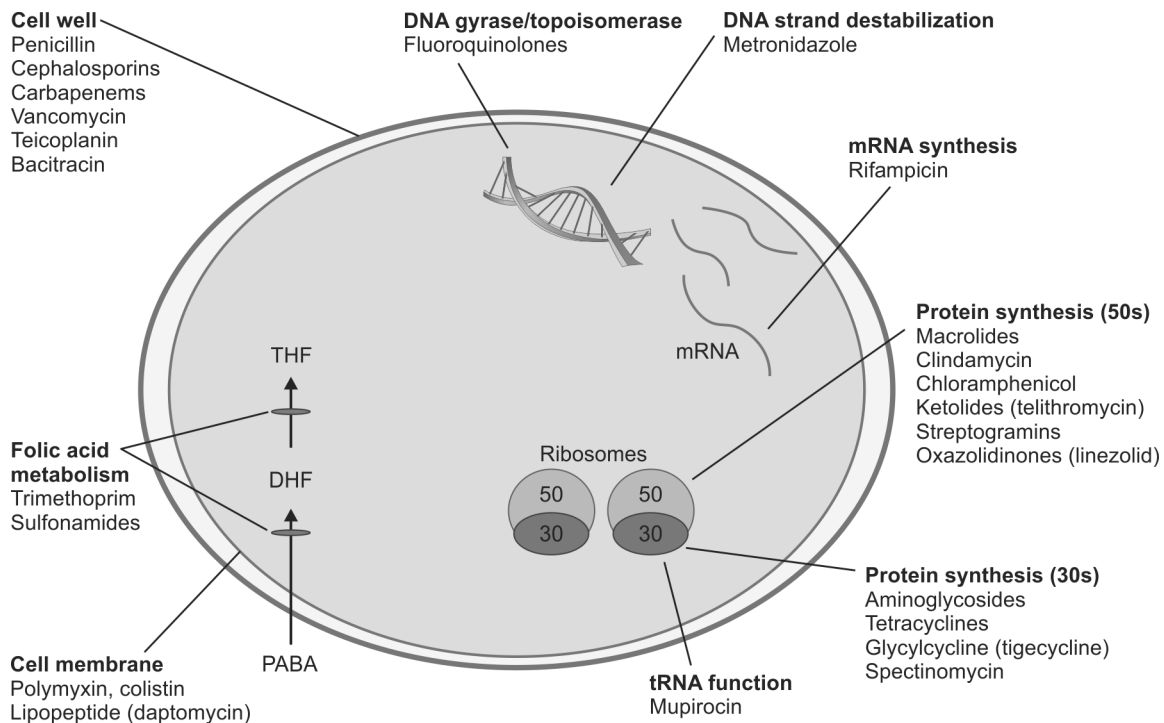


Figure 1 Illustration of a bacterial cell showing sites of action for major antibiotics

Abbreviations: PABA, para-aminobenzoic acid, DHF, dihydrofolate, THF, tetrahydrofolate.

(Adapted from Neu HC, *Science* 1992;257:1064-1073; with additional inputs from Hancock RE, *Lancet Infect Dis*, 2005 Apr;5(4):209-18.)

use of a single agent, such as a beta-lactam, or aminoglycoside alone may be associated with emergence of resistant strains, and hence dual-combination therapy is recommended.

Inhibition of beta-lactamases

Certain bacteria, such as *Staphylococcal* species secrete beta-lactamases, enzymes that inactivate beta-lactam agents such as penicillin or amoxicillin. The coadministration of a beta-lactam inhibiting agent, such as clavulanic acid or tazobactam protects the antibiotic from degradation, thus retaining efficacy and also extending the spectrum of activity of the original antibiotic.

Synergy

Synergism occurs when the combined effect of two or more drugs is significantly greater than the independent effects of the drugs when used individually. The combination of a sulfonamide with a dihydrofolate reductase inhibitor such as trimethoprim is an example of synergy brought about by inhibition of consecutive steps in the folic acid pathway, that results in reduced MIC and enhancement of the combination antimicrobial's bactericidal activity. Another example is streptogramin antibiotics (quinupristin-dalfopristin) that act in concert on bacterial ribosomes, resulting in antibacterial activity when co-administered. Synergism can also occur when cell wall-active agents are used in conjunction with ribosomal-active agents. A beta-lactam antibiotic that acts on the cell wall can enhance the entry of an aminoglycoside, thus producing bactericidal synergy against certain organisms. This type of synergy is seen with enterococci, staphylococci, viridans streptococci and *Pseudomonas* species. For instance, in enterococcal endocarditis, penicillin in combination with gentamicin results in much higher clinical cure rates than when penicillin is used alone.

Alteration of Pharmacokinetics

A mechanism that increases levels or maintains high levels for a longer duration can also have a significant effect on the antimicrobial efficacy. A classic example is the addition of probenecid that has no intrinsic antimicrobial activity, yet delays renal excretion of penicillin, thus increasing the time above MIC at the site of infection. Cilastatin, in combination with imipenem, inhibits renal degradation of imipenem, and this increases its serum half-life and, therefore, efficacy.

ADVERSE REACTIONS TO ANTIMICROBIAL AGENTS

While prescribing any therapeutic agent, an important consideration is the presence of adverse effects related to the drug. Direct adverse effects may be a result of allergy, toxicity or drug-drug interactions (**Table 2**).

Allergic or hypersensitivity reactions usually constitute *immediate* (IgE-mediated) reactions. There may also be *delayed* reactions, often manifested as a skin rash. The most severe manifestation of IgE-mediated allergy is anaphylaxis. Elicited history for allergies is not very reliable; however, a negative skin test can reliably exclude the possibility of developing an IgE-mediated

Table 2 Classification of adverse effects of antibiotics

Direct
Allergic reactions
Toxicity
Drug-drug interaction
Indirect
Effects on commensal flora (<i>Clostridium difficile</i> infection)

reaction such as anaphylaxis and can help optimize antibiotic use. This method is often employed prior to prescription of parenteral penicillin.

Drug toxicity is usually associated with higher drug doses or prolonged use, and is particularly prominent when there is underlying organ dysfunction that results in impaired drug clearance. An example is nephrotoxicity associated with aminoglycosides. In vulnerable patients, the drug doses are often adjusted to minimize drug toxicity. Therapeutic drug level monitoring with dose adjustment during prolonged dosing schedules is a modality that may be used to ensure safe serum levels of the drug.

Drug interactions with concurrently administered drugs can increase or decrease serum levels and effects of the antimicrobial agent. Many such interactions are mediated via the cytochrome P450 enzyme system. For example, rifampicin is a powerful inducer of the cytochrome P450 enzymes, increasing metabolism and thus decreasing levels of concurrently prescribed drugs. Macrolides inhibit the cytochrome P450 enzymes, subsequently increasing levels of other drugs such as the prokinetic cisapride, resulting in a dangerous risk of cardiac arrhythmias. In addition, certain drug combinations can also cause additive toxicity, as shown by the concomitant use of amphotericin and gentamicin, which can significantly increase the risk of nephrotoxicity.

Indirect adverse effects include the inhibition of normal gastrointestinal bacterial commensals, resulting in the overgrowth of pathogens, leading to *Clostridium difficile* mediated diarrhea.

ANTIMICROBIAL RESISTANCE: MECHANISMS AND DETECTION (ALSO SEE CHAPTER 27.3)

What drives antimicrobial resistance? The widespread and often injudicious use of antimicrobial agents is an important cause of emergence of drug resistance in the hospital and community settings. Other factors include incorrect dosing, and poor adherence to prescribed antibiotics.

Mechanisms of Antimicrobial Resistance

Intrinsic resistance can be attributed to inherent properties of the bacterial pathogens that render them resistant. Some examples include *Mycoplasma* species that are inherently resistant to penicillin due to the lack of a cell wall.

Acquired resistance occurs from horizontal transfer of resistance genes from other organisms. Gene sequences that bring about this horizontal transfer include plasmids, transposons and gene cassettes. Multiple mechanisms may act in concert, resulting in drug resistance. For example, *E. coli* can become resistant to multiple agents by acquiring chromosomally-mediated, or plasmid-encoded beta-lactamases, and up regulation of efflux pumps. Basic mechanisms that lead to bacterial resistance to antimicrobial agents include the following: (1) alteration of the antimicrobial binding site; (2) enzymatic inactivation or alteration, active efflux, and alterations in membrane permeability to prevent antimicrobial entry.

Detection of Antimicrobial Resistance

Understanding whether an antibiotic has adequate antibacterial activity against the suspected pathogen is critical for ensuring successful therapy. In some situations, susceptibility testing may be unnecessary, as in the case of infection with *Streptococcus pyogenes*, which is well-known to be exquisitely susceptible to penicillin. The MIC value provides an operational definition of the bacterial strain's intrinsic antibiotic susceptibility, incorporating all the additive effects of multiple mechanisms of resistance. The MIC values at which an organism is considered *susceptible* (S), *intermediate* (I) or *resistant* (R) are called breakpoints. A report of S indicates that treatment with

standard approved doses of the antibiotic should be expected to lead to clinical success as long as the tissue concentration of the antibiotic is similar to the serum concentration. A report of R suggests that microbiological cure is not achievable, as the antibiotic does not inhibit the bacterial pathogen at the standard dosing rate. MICs can have limitations and can vary according to site of infection. For example, an isolate of *Staphylococcus aureus* may be reported as susceptible to cefazolin in vitro based on the MIC; however, if this particular isolate was obtained from the cerebrospinal fluid (CSF), cefazolin would be a poor therapeutic choice because it does not achieve therapeutic concentrations in the CSF.

Different types of susceptibility tests include the disc diffusion test (Kirby-Bauer), an antibiotic strip gradient-diffusion test (E-test), agar dilution with a mechanized inoculator, broth macrodilution or microdilution test. Automated commercial test systems are also available. In addition to these traditional methods, molecular detection of bacterial resistance is gaining popularity. These susceptibility tests have been standardized and provided with standard thresholds and interpretations by the Clinical and Laboratory Standards Institute (CLSI), a nonprofit global organization that develops susceptibility standards through extensive laboratory testing and clinical correlation. Certain modified tests may be used in order to detect specific types of resistance in pathogens that have special clinical significance. Examples include disc diffusion testing for ESBL detection (**Fig. 2**) and PCR-based testing for *mecA* gene in resistant *Staphylococcus aureus*.

Prevention of Emergence of Antimicrobial Resistance

This can be achieved through judicious antibiotic prescribing (**Box 2**), whose important components include restraint of antibiotic treatment for community-acquired, mostly viral, upper respiratory tract infections; use of narrow-spectrum antibiotics when possible; and use of antibiotics for the shortest duration that is effective for bringing about improved clinical outcomes. The use of rapid diagnostic tests and biomarkers can also help toward better diagnosis of viral infections, and toward more careful use of empiric antibiotics in these settings.

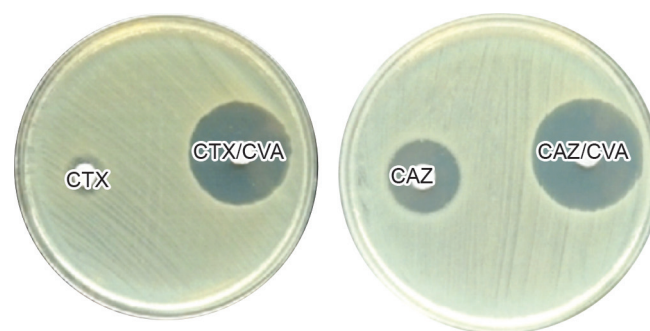


Figure 2 Disc diffusion testing for extended spectrum beta-lactamase (ESBL) production in *Klebsiella pneumoniae* lawn culture in a petri dish. The inhibition zone around the ceftazidime/clavulanic acid-containing disc (CAZ/CVA) is larger than that around the disc containing the corresponding cephalosporin alone (CAZ). An increase of 5 mm or more around the beta-lactam/beta-lactamase disc is indicative of ESBL production

Abbreviation: CTX, ceftioxiime.

(Adapted from teaching slides, Infectious Diseases Unit, St John's Research Institute, Bangalore).

BOX 2 Tips for prescribing antibiotics*For outpatients*

- Limit prescribing over the telephone to exceptional cases where there is a strong evidence of clinical benefit
- Consider a nonantibiotic strategy for common upper respiratory infections, such as acute cough, common cold and acute sinusitis
- When prescribing an antibiotic, always pay attention to the dose and the duration
- Avoid overuse of broad spectrum antibiotics (e.g., amoxicillin-clavulanic acid, quinolones and cephalosporins) as this can increase risk of resistant infections, and can also limit the future usefulness of these agents. Consider use of narrow spectrum agents (e.g., penicillin, amoxicillin, trimethoprim) for specific indications when clinically appropriate
- Avoid widespread use of topical antibiotics (especially those agents also available as systemic preparations, such as colistin and fusidic acid)

For inpatients

- Define the infection in three possible ways: anatomically, microbiologically and pathophysiologically
- Obtain microbiological cultures before starting antibiotics
- Use imaging, rapid diagnostics and special procedures early in the course of infection
- Do not rely solely on *response to therapy* to guide therapeutic decisions; follow recommended guidelines
- If empiric therapy is started, reassess at 48–72 hours, and proceed to targeted therapy as soon as possible by de-escalating antibiotics
- Check drug doses and interactions with co-administered drugs
- Document antibiotic start date and planned duration of treatment clearly.

ANTIMICROBIAL STEWARDSHIP (ALSO SEE CHAPTER 27.3)

Overuse of antimicrobials can ultimately be a threat to their effectiveness. The emergence and spread of antimicrobial resistance complicates therapy, raises costs and increases the likelihood of treatment failure. Antimicrobial stewardship programs are aimed to optimize selection of antimicrobials, restrict their inappropriate use, optimize dose, route and duration of treatment for best outcomes, limit costs, adverse events and emergence of resistance. Typically, a multidisciplinary team constitutes the antimicrobial stewardship program, consisting of an infectious disease physician, clinical microbiologist, clinical pharmacologist, infection control nurse and hospital administrator. Critical components of antimicrobial stewardship include the following: prospective

audit and feedback of antimicrobial prescriptions to clinicians, formulary restriction, education, use of clinical guidelines, de-escalation of therapy, and expeditious conversion of antimicrobial from intravenous to oral route when appropriate.

IN A NUTSHELL

1. Antibiotics are remarkable tools that have played a spectacular role in maintaining health and prolonging life.
2. Prescribing an antibiotic in the most appropriate manner possible is a serious responsibility that health workers should collectively shoulder.
3. This task involves having an acute knowledge of the costs, risks and benefits of antibiotic use, making an informed and accurate diagnosis, determining the need for and timing of antibiotic therapy, understanding dosing effects, tailoring treatment to host characteristics, using the narrowest spectrum and shortest duration of therapy, and switching to oral agents as soon as possible.
4. Teamwork is essential in these activities, and these principles of antibiotic use may be pursued diligently to provide the best possible care for patients.

MORE ON THIS TOPIC

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Chapter 29.3

Diphtheria

Prerna Batra, Piyush Gupta

Diphtheria is an acute infectious disease, caused by a toxin producing bacillus *Corynebacterium diphtheriae*. The classic presentation is respiratory disease characterized by formation of pseudomembrane over tonsils. Uncommonly, the disease can also affect skin, eyes, ears or genitals. The patient usually presents with fever and signs localizing to the affected organ system. Asymptomatic human carriers are the reservoirs for the bacilli. Despite good coverage with vaccination in developed countries, diphtheria continues to occur with breach of immunization. The disease is endemic in developing countries from Africa, Latin America, Asia and Middle East.

EPIDEMIOLOGY

Diphtheria is prevalent worldwide. Number of cases, morbidity and mortality declined following introduction of vaccine in the late 1940s. In the United States, epidemics occurred during 1990s, with case fatality rates varying from 3 to 23%. After 2003, no case of respiratory diphtheria has been reported from the US, a significant change in epidemiology. Outbreaks keep on occurring in developing countries. A major outbreak was reported from countries of Soviet Russia in 1990s. Nigeria had a major outbreak of diphtheria in 2011, where none of the 98 patients affected were vaccinated. A shift of the disease towards adult patients has been noticed due to waning immunity with increasing age. In India, diphtheria is an endemic disease, though showing a decrease in number of cases because of widespread coverage of vaccination. Peak incidence is the cooler months of autumn, winter and spring season.

ETIOLOGY

Corynebacterium diphtheriae is an aerobic gram-positive pleomorphic bacillus. When grown on a special medium (Löeffler's medium), it exhibits a characteristic club shape. The organism can also be readily grown in tellurite cysteine medium (tellurite).

Corynebacterium diphtheriae produces a powerful exotoxin, responsible for its virulence. Diphtheria toxin is a 58 kDa polypeptide, containing fragment A (21 kDa) and fragment B (37 kDa). Fragment A is the biologically active form that catalyzes transfer of adenosine diphosphate ribose (ADPR) from nicotinamide adenine dinucleotide (NAD) to elongation factor 2 (EF-2). Fragment B contains the receptor-binding domain that is responsible for passage of toxin through the target cell. *C. diphtheriae* strain can be either toxigenic or nontoxigenic, depending on its ability to be lysogenized by *tox*⁺ gene carrying corynephage. *Corynebacterium ulcerans* and *Corynebacterium pseudotuberculosis* strains are capable of producing diphtheria toxin and clubbed under *C. diphtheriae* group. Cardiac, renal and neurological sequelae are observed following infection with toxigenic strains only, whereas nontoxigenic strains lead only to sore throat and rarely invasive infections.

Four biotypes of the organism are reported: mitis, intermedius, gravis and belfanti. Gravis biotype is considered to be most toxigenic. Olu, *et al.* identified eight genotypes of the organism by multilocus DNA sequencing (MLST) in Russia between 2002 and 2012. Most of the toxic strains belonged to gravis biotype and ST 8 genotype.

PATHOGENESIS

Corynebacterium diphtheriae gains entry into human body via oral or nasal route either through direct contact or through droplet infection. The organism is carried in the upper respiratory tract or skin of asymptomatic carrier. At times, ocular or genital tract may also harbor the microbe. Incubation period is 2–7 days. After this incubation period, the organism starts producing toxin. The primary local lesion consists of necrotic injury to epithelial cells in the upper respiratory tract. As a result of this injury, blood plasma leaks into the area and a fibrin network forms, which is interlaced with rapidly-growing *C. diphtheriae* cells. This membranous network covers the site of the local lesion and is referred to as the *pseudomembrane*. This is a whitish, tough membrane that is adherent to underlying tissues and is difficult to remove. Over a period of days, it becomes gray and later on develops green or black spots, because of necrotic areas.

The diphtheria bacilli do not tend to invade tissues below or away from the surface epithelial cells at the site of the local lesion. At this site, the toxin produced is absorbed and disseminated through lymph channels and blood to the susceptible tissues of the body. Degenerative changes in these tissues, which include heart, muscle, peripheral nerves, adrenals, kidneys, liver and spleen result in the systemic pathology of the disease. Cardiac manifestations appear after a latent period of 10–14 days and CNS manifestations after 3–6 weeks. Histologic studies of the cardiac tissues have shown necrosis, hyaline degeneration, mononuclear infiltration and fatty accumulation in the myocardium. Affected nervous tissue is characterized by degenerative changes in the myelin sheath and axons. These changes lead to peripheral neuritis in children with diphtheria. Necrosis and hyaline changes may be seen in liver. Acute tubular necrosis may occur in kidneys of the affected individual.

CLINICAL FEATURES

Centre for Disease Control (CDC), USA classifies diphtheria into various clinical manifestations depending upon the site of involvement. A review of 676 cases of diphtheria from Kyrgyz republic during an outbreak from 1994 to 1998 showed that 28% of patients had tonsillar presentation and 30% had severe forms of diphtheria.

Anterior Nasal Diphtheria

It is a relatively milder form of disease, more commonly seen among infants and younger children. Child presents with mild fever, sore throat and mucopurulent nasal discharge. Pseudomembrane develops over the nasal septum, which sloughs off leading to blood-tinged discharge.

Pharyngeal and Tonsillar Diphtheria

It is the commonest form of diphtheria. The illness is characterized by insidious onset with sore throat, fever, malaise and loss of appetite. After 1 or 2 days, exudate appears adjacent to tonsils that coalesce to form a pseudomembrane covering pharynx, tonsils and uvula. Associated cervical lymphadenopathy also develops. The child may develop marked edema of anterior neck, giving characteristic 'bull neck' appearance. Features of upper respiratory tract obstruction may develop in the form of dysphagia, drooling of saliva, and difficulty in breathing. A more severe and toxic form of presentation with rapid deterioration leading to respiratory and circulatory collapse may also occur.

Laryngotracheal Diphtheria

Laryngotracheal diphtheria is a severe form of diphtheria where patient is more prone to respiratory compromise. This occurs as a result of downward spread of membrane from pharynx. These patients present with noisy breathing, stridor, hoarseness of voice and dry cough. The illness becomes fatal if respiratory obstruction is not rapidly relieved.

Cutaneous, Ocular and Genital Diphtheria

Cutaneous diphtheria It is more common in overcrowded conditions and in tropical states. Though the lesion does not have a characteristic appearance, it is usually an ulcerated painful lesion, with ill-defined margins, surrounding erythema and membrane. Healing takes 2–3 months but rarely may persist for a year.

Ocular Diphtheria Ocular lesions are characteristically conjunctival lesions, mainly over the palpebral conjunctiva.

Genital Diphtheria Vulvovaginal form of disease is also seen. Other rare presentations of disease include meningitis, osteomyelitis, arthritis and hepatitis.

COMPLICATIONS

The toxin elaborated by diphtheria bacillus can cause damage to cardiac, neural and renal tissue. The extent of secondary damage depends upon the severity and extent of the primary disease and amount of antitoxin circulating in the body.

Myocarditis Myocarditis is seen in 10% of affected patients. It usually develops during 1st week of illness and leads to dysrhythmias and cardiac failure. The child has tachycardia and muffled heart sounds.

Neuritis Neuritis affecting motor nerves is seen in 75% of severe cases. Neural involvement starts in the 2nd week of illness with palatal involvement and then descends to involve pharyngeal, laryngeal and diaphragmatic muscles. This disease progresses till 6th week of illness. During the course of disease, patient may succumb due to respiratory complications. Recovery starts after a few weeks. The manifestations start with a nasal twang in voice, nasal regurgitation, dysphagia and drooling of saliva. Loss of accommodation and difficulty in vision develops with ocular muscle involvement. Motor weakness is symmetrical and simulates Guillain-Barre syndrome. Neural complications are self-limiting.

Renal failure Child may rarely develop renal failure as a complication of diphtheria which is often fatal. A report from Chandigarh, India showed renal failure in 17 out of 48 patients, out of which 15 died, though they were shown to have coexistent myocarditis and cardiogenic shock.

Other reported complications of diphtheria include endocarditis, thrombocytopenia leading to skin bleeds, otitis media, and subcapsular hemorrhage in spleen.

DIFFERENTIAL DIAGNOSIS

Diagnosis of diphtheria is often clinical. In emergency setting for the purpose of prompt initiation of specific management, it needs to be differentiated from some other common illnesses seen in children. Differential diagnoses are usually pertaining to the site of involvement.

Nasal diphtheria in its milder form resembles common cold. Other conditions that may mimic the condition are snuffles, foreign body, sinusitis and adenitis. Streptococcal sore throat closely resembles pharyngeal diphtheria. Acute onset, high grade fever and absence of pseudomembrane help differentiate the condition. The clinical picture may at times be confused with

infectious mononucleosis and Vincent's angina. Other differential diagnoses include viral pharyngeal infections, like herpetic tonsillitis, adenovirus and cytomegalovirus infection. Laryngeal involvement in diphtheria needs differentiation from croup and croup-like illnesses, epiglottitis and foreign body. Genital lesions in an adolescent may be confused with sexually transmitted diseases. Neurological complications of diphtheria mimic acute flaccid paralysis because of Guillain-Barré syndrome.

APPROACH TO DIAGNOSIS

A careful history including the onset and progression of symptoms, and examination with visualization of pseudomembrane helps in establishing the correct diagnosis. Supportive laboratory investigations further help. The diagnosis is finally confirmed by isolation of organism from the lesion.

Culture of the Organism

In suspected cases, an attempt should be made to obtain a specimen for staining and culture of the organism from the site of infection. The swab can be obtained from nasopharynx, oropharynx, tonsils, cutaneous or genital lesions. Multiple, inflamed areas should be swabbed. If pseudomembrane is seen, the sample should also be taken from the area beneath the membrane. It is important to inform the laboratory regarding the suspicion of diphtheria in advance, so that appropriate culture media are used. As the bacteria are relatively resistant to drying, it may be transported to laboratory in Amies medium. Swab is plated on Löeffler's medium or tellurite. After 8–18 hours, staining of the growth with methylene blue reveals club-shaped diphtheroid cells containing metachromatic granules. *Elek test* should be performed on the organism isolated to test for toxigenicity. The test is based on gel diffusion and immunoprecipitation technique. The results are available in 48 hours.

Rapid Diagnostic Tests

Enzymatic assay to detect diphtheria toxin by using equine polyclonal antibody is now available. The test is rapid and gives diagnosis in 3 hours. Polymerase chain reaction (PCR) for detection of either 'A' or 'B' portion of *tox* gene is also available. The concern with these tests is the cost associated with these and poor availability.

Other Hematological and Biochemical Tests

These tests do not have a role in establishing the diagnosis. Presence of leukocytosis (TLC > 25,000/μL) has prognostic value. Thrombocytopenia may be seen in patients with complications of diphtheria and disseminated intravascular coagulation (DIC). Hemoglobin may be on lower side of normal range. Hepatic complications may lead to hypoglycemia, glycosuria and raised liver enzymes. Blood urea nitrogen (BUN) and creatinine are elevated in presence of acute tubular necrosis. Cerebrospinal fluid (CSF) examination reveals raised protein levels, but cell count and sugar levels are normal. Cardiac complications may reveal ECG changes in the form of tachycardia, low voltage and arrhythmias.

MANAGEMENT

Specific treatment with *antitoxin* and *antibiotics* should be initiated immediately while bacteriological investigations are still pending. Antitoxin therapy is the mainstay of therapy. Antibiotic therapy is required to eradicate the organism and prevent spread. Mechanical airway obstruction and myocarditis are the main causes of death in toxigenic disease and careful supportive management is required.

Specific Therapy

Diphtheria Antitoxin

Diphtheria antitoxin is hyperimmune serum produced in horses. Antitoxin will only neutralize circulating toxin that is not yet bound to tissue, thus prompt administration is critical. Delayed administration increases the risk of late effects, such as myocarditis and neuritis. Before antitoxin is administered, the patient should be tested for sensitivity to horse serum and, if necessary, desensitized. Sensitivity testing is done by administering 0.02 mL of 1:1000 dilution of antitoxin intradermally. Alternatively, 1:10 dilution of antitoxin can be instilled into conjunctival sac or a drop can be administered intradermally in 1:100 dilution. If there is a sensitivity reaction, desensitization is required. Desensitization is done by giving slowly increasing dosages of antitoxin every 15 minutes intravenously. To start with, 1:1000 dilution is used, which is gradually increased to undiluted antitoxin. If acute anaphylaxis develops, intravenous epinephrine (0.2–0.5 mL of 1:1000 solution) be administered immediately by intravenous injection.

The dose of antitoxin to be administered depends upon the site and extent of the diphtheritic membrane, the degree of toxicity and the duration of illness. **Table 1** indicates the suggested dose range for various clinical situations. Role of antitoxin in cutaneous form of disease is controversial, although some centers advocate 20,000–40,000 units of antitoxin because toxic sequels have been reported.

Table 1 Dosage of antitoxin recommended for diphtheria

Type of diphtheria	Dosage (units)	Route
Nasal	10,000–20,000	IM/IV
Tonsillar	15,000–25,000	IM/IV
Pharyngeal or laryngeal	20,000–40,000	IM/IV
Combined types or delayed diagnosis	40,000–60,000	IV
Severe diphtheria with respiratory obstruction or bull-neck	40,000–1,00,000	IV or part IV and part IM

Abbreviations: IV, intravenous; IM, intramuscular

Antibiotics

Antibiotic treatment is necessary to eliminate the organism and prevent spread; it is not a substitute for antitoxin treatment. The antibiotics of choice are penicillin or erythromycin. Additional advantage of using penicillin is that it is also effective against Group A β hemolytic *Streptococcus*, which complicates almost one-third of these patients.

Crystalline penicillin (1,00,000–1,50,000 units/kg/day in four divided doses) intravenously or procaine penicillin G (25,000–50,000 units/kg/day in two divided doses) intramuscularly are the initial therapeutic options. One can shift to oral erythromycin (40–50 mg/kg/day in 4 divided doses) or oral penicillin V (125–250 mg twice daily) when the patients is able to swallow. Antibiotic treatment should be continued for 14 days. The organism shows in vitro susceptibility to other drugs, like clarithromycin, azithromycin, amoxicillin, rifampin and clindamycin also, but their role in treatment of the disease is not yet proven.

The treatment should be followed by repeating culture 2 weeks after completion of antibiotics. If culture still remains positive, additional course of erythromycin should be given for 10 days. Two to three consecutively negative cultures taken 24 hours apart suggest the cure.

Treatment of Carriers

Carriers should be treated with erythromycin 40 mg/kg/day for 7–10 days or a single intramuscular dose of benzathine penicillin (0.6 mega units for < 30 kg weight and 1.2 mega units for > 30 kg). Cultures should be obtained after two weeks. If positive, give an additional course of erythromycin for 10 days.

Unimmunized carriers should receive a full schedule of active immunization. Previously immunized carriers should receive a booster dose if the previous dose was received more than a year ago.

Supportive Therapy

Diphtheritic infection has a high likelihood of letting into life-threatening complications as discussed earlier. Management of ABC (airway, breathing and circulation) should be prime importance. Frequent suctioning of secretions to prevent aspiration should be done. Patient should be monitored for oxygen saturation by pulse oximetry, and oxygen supplementation should be provided, if there is hypoxia. Ventilation should be supported if required. Intravenous fluids should be given and monitoring for earliest evidence of shock be done. In stable patients also, bedrest is required for at least 2–3 weeks. Child should be monitored carefully for development of complications for 4–6 weeks. Serial ECG monitoring may be done.

PROGNOSTIC FACTORS

Diphtheria carries a high case fatality rate. Immunization status of the host remains the most important prognostic factor. Early initiation of antitoxin therapy markedly improves the outcome. The disease is likely to be more fatal among infants and older age group of patients. Toxigenicity of the agent, i.e., *C. diphtheriae* is found to relate with the severity of complications. Nontoxigenic strains may cause the disease, but complications like myocarditis, neuritis and renal failure do not occur as these are toxin-mediated. Amongst toxigenic strains, *gravis* is the most severe of all. Presence of leukocytosis, thrombocytopenia and other systemic complications mark a poorer prognosis.

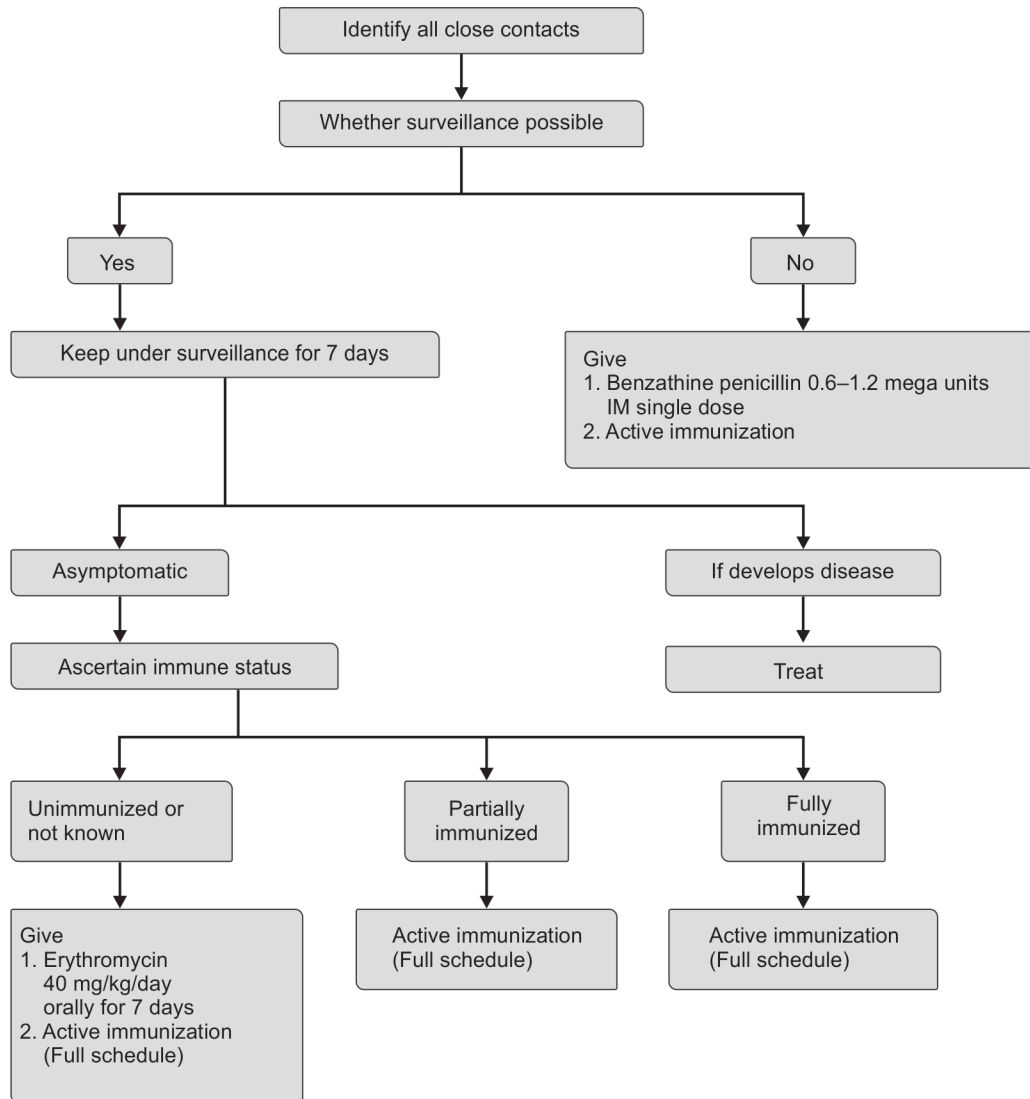
PREVENTION

Isolation of the patient Communicability in untreated persons lasts for two weeks, and in treated adequately, for less than four days. The patient should be isolated until this period is over or two cultures from nose and throat are negative.

Care of the contacts Management of close contacts is given in the **Flow chart 1**. There is no role of prophylactic diphtheria antitoxin in unimmunized close contacts.

Active immunization Currently available diphtheria vaccine is a toxoid, available as DPT vaccine. **Primary immunization** consists of three doses at an interval of 4–6 weeks, starting from 6 weeks after birth. First booster is given at 18 months and a second booster at 5 years. Subsequent boosters are not necessary in India where *C. diphtheriae* infection is common. If the primary immunization is to be carried out in adult or older child, the adult type of toxoid (Td) containing less quantities of antigen should be employed.

In the light of recent diphtheria outbreaks affecting older children and younger adults in developing countries and the resurgence of the disease in industrialized countries, it has become clear that periodic administration of booster doses of diphtheria toxoid is needed to ensure long-lasting protection of all individuals against diphtheria. Thus, TT should be replaced with Td in a phased manner.

Flow chart 1 Care of contacts of a patient with diphtheria**IN A NUTSHELL**

1. Diphtheria is a potentially fatal disease caused by exotoxin producing bacteria *C. diphtheriae*.
2. Presence of pseudomembrane on the affected site is pathognomonic of the disease.
3. Diphtheria may have various clinical presentations, namely nasal, pharyngeal and tonsillar, laryngeal, cutaneous, ophthalmic or genital.
4. Pharyngeal diphtheria is commonest and these patients have a high likelihood of developing respiratory failure.
5. Myocarditis, neuritis and renal failure are potential complications, for which patients need close monitoring.
6. Diagnosis is established by isolation of organism in special culture media.
7. Patients need to be started with antitoxin on the basis of clinical diagnosis as soon as possible.
8. Main role of antibiotics, i.e., crystalline penicillin and erythromycin is to prevent further transmission of the disease.
9. Carriers and close contacts should be managed as per the standard protocols.
10. Primary immunization with diphtheria toxin is a must for prevention.

MORE ON THIS TOPIC

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Chapter 29.4

Pertussis

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Pertussis is a highly communicable disease of respiratory tract caused by *Bordetella pertussis*, and at times by *B. parapertussis*. The disease is characterized by paroxysms of cough and a peculiar inspiratory sound *whoop*. Pertussis is known to affect all the age groups, but more often diagnosed in young children. Infants less than 3 months of age carry poor prognosis. The disease is endemic worldwide.

EPIDEMIOLOGY

Pertussis is highly infectious, with secondary attack rate up to 90%. Outbreaks of pertussis are reported since 16th century. The number of outbreaks declined after 1940, after the introduction of whole cell pertussis vaccine. However, disease resurgence was noticed in 1980s all over the globe. This pattern has been seen in all parts of the world; Australia, Netherlands, United Kingdom, United States, Italy and Brazil just to name a few. South Asian countries have shown a similar trend, with major outbreaks reported from Afghanistan, Thailand, Israel and Taipei. In 2007, an outbreak was reported from Arunachal Pradesh in India, with attack rate of 30%. Possible reasons for this resurgence are increased vaccine failures from genetic changes in *B. pertussis*, waning immunity, better diagnostic abilities due to better laboratory facilities, and greater awareness of the disease. Another important reason being considered is shift from whole cell vaccine to a less potent acellular vaccine. The contributions of these reasons, however, vary in different regions of the world. Another trend reported in recent years is shift to adolescents and adults.

Man is the only reservoir for *B. pertussis*. Transmission of infection occurs mainly via direct contact or through droplets by coughing. Pertussis cases are seen throughout the year; still a rise in number is observed during summer and fall in most of the regions. The transmission increases with overcrowding, poor hygienic conditions and close contact. Asymptomatic carriers exist and carry infection for a short duration. A female preponderance is seen for reasons unknown.

ETIOLOGY

Bordetella pertussis is the causative organism in more than 95% of cases, with remaining few caused by *B. parapertussis*, *B. bronchiseptica*, and *B. holmesii*. *B. pertussis* is an aerobic, gram-negative, pleomorphic coccobacillus. It contains a variety of biologically active and antigenic substances. These include fimbriae (FIM), filamentous hemagglutinin antigen (FHA), pertactin (PRN), other surface-associated proteins like Vag8, BrkA, Sph B1, tracheal colonization factor (tcfA), pertussis toxin (PT), adenylate cyclase toxin (ACT), dermonecrotic toxin (DNT), tracheal cytotoxin, and lipopolysaccharide (LPS) endotoxin. Fimbriae are highly immunogenic and antibodies to them, along with other antigens, cause agglutination of the organism. FHA is also an immunogenic component of cell wall of *Bordetella* species and is the component of most acellular vaccines. Pertussis toxin produced by *Bordetella* adversely affects host immune functions and is responsible for severity of morbidity associated with the illness. It also contributes to lymphocytosis. ACT, DNT and tcfA cause local damage to respiratory tract.

Virulence of *B. pertussis* is regulated by a single gene *bvgAS*. In the presence of favorable conditions, this gene is activated (*bvg+*) and leads to formation of various antigens and toxins except tcfA. The phenomenon has been proven in animal models.

PATHOGENESIS

Infection with *B. pertussis* is followed by attachment of bacteria to respiratory tract epithelium, evasion of host defense, local damage, and systemic disease. Attachment is mediated by various adhesins present on the surface of *Bordetella* as described above. Ciliary damage to the respiratory epithelial surface initiates inflammation. There is interference of pulmonary secretion clearance. Histopathology of lung tissue after autopsy from 15 infants with fatal pulmonary pertussis infection showed necrotizing bronchiolitis, intra-alveolar hemorrhage and fibrinous edema. PT causes lymphocytosis and deterioration in cell-mediated immunity. Incubation period is 7–10 days, and may extend up to 3 weeks.

CLINICAL FEATURES

Severity of clinical features depends on various factors, which include age, immunization status, passively acquired immunity, degree of exposure and genotype of the organism. Classically, the disease is characterized by three distinctly identifiable stages.

1. Catarrhal Stage

Disease manifestations start with a mild respiratory illness, resembling common cold. Patient has mild fever, running nose, sneezing and mild cough. Catarrhal stage lasts for 1–2 weeks. Symptoms may be minimal among young infants during this stage.

2. Paroxysmal Stage

This is the stage of classic presentation of pertussis when most of the cases are identified. The child presents with increased severity of cough that occurs in bouts. At the end of the bout, patient forcefully inspires through a narrow glottis producing the characteristic *whoop*. Paroxysm is associated with cyanosis, suffusion of the face, bulging eyes, protrusion of tongue, excessive salivation, lacrimation and post-tussive vomiting. Patient may have several spasms during a span of 24 hours. The patient gets exhausted and has difficulty in feeding during spasms, though appears comfortable in between these bouts of cough. The stage may last for 1–6 weeks.

3. Convalescent Stage

During this stage, spasms become less frequent and severity of coughing decreases. Clinically, it may be difficult to clearly differentiate it from paroxysmal stage. This stage may last up to 3 months. The disease is, therefore, a prolonged course, with cough being the prominent feature, commonly called *cough of 100 days*.

Previously vaccinated children may have a mild, nonclassic illness. Yaari, *et al.* studied the profile of serologically confirmed pertussis patients from Israel. Mean duration of cough was 23 days, with majority not having the whoop.

In infants, pertussis has an atypical presentation. Manifestations depend on the age of presentation, immunization status and levels of transplacentally acquired antibodies. The baby may develop choking, gasping, apnea and bradycardia as a result of severe spasm of cough. Whoop may be absent in these patients. Young infants also develop difficulty in feeding and this prolonged illness along with feeding difficulty may lead to failure to thrive.

Complications

Complication rate with pertussis is very high among infants less than 6 months of age. These complications mostly are either because of the violent cough or may be pulmonary or neurological. Severe spasmodic cough in the stage of paroxysms may lead to rupture of alveoli and development of subcutaneous emphysema. The patient may even develop subconjunctival bleed, subcapsular bleed, subdural bleed, umbilical hernia and inguinal hernia. At

times, the intensity of cough may be strong enough to even lead to rib fracture.

Pulmonary complications include pneumonia, otitis media and pulmonary hypertension, whereas neurological complications include seizures, encephalopathy and polyneuropathy. The complications occur either due to *Bordetella* per se or as a result of secondary bacterial infection, or may even be because of severe hypoxia. Organisms that have been isolated from patients with secondary bacterial infection include *S. pneumonia* and *Mycobacterium tuberculosis*.

Recurrent vomiting may cause metabolic alkalosis, dehydration and failure to thrive.

DIFFERENTIAL DIAGNOSIS

Clinical diagnosis of pertussis is suspected on the basis of severe spasmodic cough, with post-tussive vomiting and apparently well child in between these spasms. But, there are certain other infectious agents that cause similar prolonged protracted cough and are often confused with whooping cough. These are mostly viral infections, like adenovirus, respiratory syncytial virus (RSV) and atypical organisms including *Mycoplasma* or *Chlamydia*. Other chronic pulmonary conditions, like hyper-reactive airway disease, cystic fibrosis and bronchiectasis, fungal or even tubercular infection may mimic pertussis. Another differential diagnosis which one must consider while dealing with a small child with prolonged cough is gastroesophageal reflux disease (GERD).

APPROACH TO DIAGNOSIS

Diagnosis of whooping cough is usually clinical and certain hematological investigation may help to support the diagnosis. Case-definition for pertussis is depicted in **Box 1**.

BOX 1 Case definition for pertussis

Suspected case

History of severe cough lasting for 2 weeks or more (84–92% sensitivity and 3–90% specificity, during outbreaks)

Probable case

Any of the following in a suspected case:

- Prolonged coughing followed by a period of apnea and cyanosis, or in older children paroxysms of coughing followed by vomiting, or a typical breath intake and 'whoop', or subconjunctival hemorrhages
- Exposure of a suspect case in the previous 3 weeks
- Epidemic of whooping cough in the area
- Lymphocytosis of $15000/m^3$ or more

Confirmed case

- Laboratory evidence of *B. pertussis* from the culture or immunofluorescence of nasopharyngeal secretions
- A case that is directly linked epidemiologically to a case confirmed by PCR or culture.

Specific laboratory diagnosis of pertussis is established by isolation of organism on appropriate medium or by documenting the presence of organism by polymerase chain reaction (PCR) or direct fluorescence antibody (DFA) testing. Culture is the gold standard for diagnosis of pertussis. Organism can be isolated from nasopharyngeal secretions obtained by aspiration or by swabbing (calcium alginate or dacron). Aspirates give best yield of organism required for the growth. Culture should be directly inoculated into *Regan-Lowe* or *Bordet-Gengou agar* media. Direct fluorescence antibody test, though rapid, has a poor sensitivity and specificity, and, hence, is no longer recommended. Leukocytosis with absolute lymphocytosis in peripheral smear also supports the diagnosis of pertussis. PCR has a better specificity than sensitivity,

especially in previously immunized patients. The sample taken is nasopharyngeal aspirate or swab, but swab should not be calcium alginate swab.

MANAGEMENT

Treatment of pertussis is primarily supportive. Adjunct therapy should center on five principles of care (**Box 2**). Affected child may look completely asymptomatic between the episodes of devastating cough. Mild sedation should be administered to allay anxiety. Humidification of the air diminishes the viscosity of mucus and the affected child can bring it out more easily. Gentle suctioning may be done. Patients should be monitored for development of complications. Severe cases may need intravenous hydration, oxygen supplementation and nutritional support. Salbutamol and corticosteroids have no role in reducing the severity of paroxysms.

BOX 2 Principles of treatment for pertussis

- Avoid provoking paroxysms of coughing
- Comforting during paroxysms
- Clearing away mucus and vomit during paroxysms to prevent inhalation
- Early recognition and treatment of complications
- Maintaining good hydration and reasonable nutrition.

Antibiotic Therapy

Antibiotics are effective only in the catarrhal stage of the disease. Once in the paroxysmal phase, drug therapy makes little impact on the course of the illness. *B. pertussis* and *parapertussis* have shown in vitro sensitivity towards many antibiotics.

Erythromycin (40 mg/kg/d orally in 4 divided doses) is considered as drug of choice against *Bordetella pertussis*. It renders the sufferer noninfectious after 5 days of treatment; however, the drug is best continued for 2 weeks as a few individuals remain culture positive even after 1 week of antibiotics. Resistance has been reported. Newer macrolides (e.g., azithromycin, clarithromycin) are potential alternatives for patients who cannot tolerate erythromycin. Azithromycin is typically administered in doses of 10–12 mg/kg/d orally once a day for 5 days. Dose of clarithromycin is 15–20 mg/kg/d orally in 2 divided doses, not to exceed 1 g/d for 5–7 days. Since use of erythromycin has been shown to be associated with idiopathic hypertrophic pyloric stenosis (IHPS) in infants younger than 1 month of age, azithromycin is the drug of choice for neonatal pertussis.

Trimethoprim-sulfamethoxazole (trimethoprim 8 mg/kg/d and sulfamethoxazole 40 mg/kg/d) in 2 divided doses is another antibiotic option, especially for infants more than 2 months of age who either cannot tolerate macrolides or have a macrolide resistant strain.

Care of Contacts

The Committee on Infectious Diseases of the American Academy of Pediatrics currently recommends promptly treating all household and other close contacts (e.g., children and staff at daycare centers) with erythromycin to limit secondary transmission. This is regardless of the age or immunization status of contacts. A 14-day course of oral erythromycin (40–50 mg/kg/d in 4 divided doses) is recommended for close contacts. Some experts prefer the estolate preparation in young infants because of more effective absorption, which may lead to decreased dosing and less frequent dosing intervals.

Patients of whooping cough remain infectious for a long time and, hence, they should remain isolated until 3 weeks after the onset of paroxysms of cough.

PROGNOSIS

Prognosis depends upon the age of the patient. Infants have a poorer prognosis with a high risk of neurological complications. Immunization status of the child is another important prognostic factor. The disease is much more severe in unimmunized and partially immunized patients.

PREVENTION

Natural disease does not provide life-long immunity. Similarly, pertussis vaccination protects the individual for a maximum period of 10–20 years. However, universal immunization of children with pertussis vaccine is essential for control of pertussis. Since protective antibodies against this disease do not cross the placenta, early immunization is desired. It has been seen that four primary doses of whole cell pertussis vaccine provide 70–90% protection against serious pertussis disease. National Immunization Schedule of India advocates pertussis vaccination as DPT (diphtheria, pertussis and tetanus, commonly known as triple vaccine) at 6, 10 and 14 weeks of age. This is to be followed by 2 boosters at 18–24 months and at 5 years of age. Whole cell vaccine (DPwT) is known to cause local reactions and mild systemic reactions. These complications are mostly due to pertussis component. There is no scientific basis to the general belief that pertussis does not affect children more than 5–6 years of age. Adult pertussis is known to occur and immunity wanes by next 6–12 years, hence, booster dose is recommended.

Acellular Pertussis Vaccine

Studies have clearly indicated that DPT with a whole cell pertussis (wP) component is responsible for frequent reactions. These reactions are both unpleasant and at times dangerous. This led to the development of acellular pertussis vaccine in the year 1981 in Japan. The acellular vaccine predominantly contains PT as the essential component, and different amounts of filamentous hemagglutinin (FHA), pertactin (PRN) and fimbrial hemagglutinins 1, 2 and 3 (FIM 1, 2, 3). Recent studies have demonstrated a better efficacy of whole cell vaccine for primary immunization, as compared to acellular vaccine (Also see Chapter 23.8 on DPT vaccine).

Indian Academy of Pediatrics (IAP) recommends use of whole cell pertussis vaccine for primary immunization. WHO also recommends continuation of the whole cell pertussis vaccine in countries with limited resources.

IN A NUTSHELL

1. Pertussis is a highly communicable disease caused by *Bordetella pertussis*.
2. It is a toxin mediated disease that causes damage to the epithelium of respiratory tract, thus inhibiting clearance of secretions.
3. Clinically, disease has three stages, namely, catarrhal stage, paroxysmal stage and convalescent stage.
4. Paroxysmal stage is characterized by spasmodic cough with inspiratory whoop.
5. Infants are more likely to develop complications of the disease.
6. Diagnosis is established by isolation of organism on *Regan-Lowe* or *Bordet-Gengou* medium.
7. Management is mostly supportive, targeted towards comforting the patient and monitoring for complications.
8. Prime role of antibiotics is to render the patient noninfective and prevent the spread of the disease.
9. All the close contacts irrespective of the immunization status should be given erythromycin.
10. Immunization with 3 doses and 2 boosters of DPT vaccine prevents pertussis with 70–90% efficacy.

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Chapter 29.5

Tetanus

Jaydeep Choudhury

(Also see Chapter 15.5 on Neonatal Tetanus)

Tetanus is an acute, often fatal, severe exotoxin-mediated infection caused by *Clostridium tetani*. The disease is characterized by severe muscle spasm. Rosenbach in 1886 demonstrated for the first time these slender bacilli.

EPIDEMIOLOGY

Tetanus occurs worldwide, but the incidence has reduced considerably following widespread immunization. Still it is an important preventable cause of neonatal death in developing countries. It is the only vaccine preventable disease that is infectious but not contagious from person to person. Among the burden of vaccine preventable diseases world over, tetanus ranks fourth with 13% disease burden. According to WHO in 2008, the reported cases of tetanus in India in 2006 were 2,587, of which 600 cases were of neonatal tetanus. The incidence is high in tropical countries with humid climate. More cases are reported from rural than urban areas.

ETIOLOGY

The causative organism *C. tetani* is a gram-positive, anaerobic, spore-forming organism. It forms terminal spores resembling drumsticks. The spores are resistant to boiling, usual antiseptics and chemical agents like phenol. They can survive autoclaving at 121°C for 10–15 minutes. *C. tetani* is part of the normal flora in human and animal intestines and is disseminated through the excreta. In spore form, they are hard and long-lasting in soil and dust. As the spores of *C. tetani* are ubiquitous, wound contamination is unavoidable. The contamination of wound, unhygienic and improper handling of the umbilical cord in newborns, lack of hygienic habits and aseptic care during and after delivery in women are the main risk factors for infection.

The bacilli itself is noninvasive. The spores germinate in anaerobic conditions. They produce two types of toxins—*tetanospasmin* and *tetanolysin*. Of these, tetanospasmin is a neurotoxin and is responsible for the clinical signs and symptoms of the disease. Toxins are disseminated via blood and lymphatics. Toxins act at several sites within the nervous system.

CLINICAL MANIFESTATIONS

The incubation period of tetanus is around 10 days (range 3–30 days). On the basis of clinical findings, three different forms of tetanus have been described. The most common type (80%) is generalized tetanus. *Localized tetanus* produces pain and spasm of the muscles in proximity to the site of injury. Occasionally this form of disease may precede *generalized tetanus*. *Cephalic tetanus* is a rare form of the disease seen in children with otitis media.

Generalized Tetanus

It usually presents with a descending pattern. The first sign is trismus or lockjaw due to spasm of masseter muscle, followed by stiffness of the neck, difficulty in swallowing and rigidity of abdominal muscles. The spasms can be precipitated by bright light, noise and even touch. Difficulty in swallowing, restlessness, irritability and headache are early manifestations. The rigidity of facial muscles leads to the sardonic smile of tetanus or risus sardonicus, a typical grinning appearance. Rigidity and spasm

of back and abdominal muscles causes arching (opisthotonus). Laryngeal and respiratory muscle spasm can lead to airway obstruction and asphyxia. Constipation and retention of urine may also occur. Hyperpyrexia, hypertension, excessive sweating, tachycardia and cardiac arrhythmia can occur due to sympathetic nerve involvement.

Neonatal Tetanus

It typically occurs when the umbilical cord is cut with an unsterile instrument and manifests within 3–12 days of birth. It is generalized tetanus, a serious condition and often fatal. Progressive difficulty in feeding (sucking and swallowing) with associated hunger and crying are generally seen. The baby becomes stiff and spasms develop. Opisthotonus may be extreme or sometimes absent. Neonatal tetanus has been already described in detail in Chapter 15.5.

MANAGEMENT

Diagnosis is mainly clinical. Differential diagnosis is listed in **Box 1**. The typical setting is an injured unimmunized patient or baby born to an unimmunized mother presenting within 2 weeks with trismus, rigid muscles and clear sensorium. The organism can be isolated from wound or ear discharge. The aim of therapy is to neutralize all toxins, eradication of *C. tetani* and wound environment conducive to anaerobic multiplication and supportive care.

Specific

Human tetanus immunoglobulin (TIG) 3,000–6,000 units IM is recommended to be given immediately. TIG has no effect on toxin which is already fixed to the neural tissue and does not penetrate the blood-CSF barrier. It can neutralize circulating tetanospasmin. Antitetanus serum is recommended only when TIG is not available. It can be given in a single dose of 50,000–1,00,000 units, half the dose IM and the rest IV after skin test.

Penicillin is the antibiotic of choice for *C. tetani*. Penicillin G 2,00,000 units/kg body weight can be given intravenously in four divided doses for 10–14 days. Local wound, discharging ears, umbilical cord should be cleaned and debrided.

Supportive

All patients with generalized tetanus require muscle relaxant. High-dose diazepam is preferred as it causes both muscle relaxation and seizure control. Midazolam and baclofen can also be used. Detailed management of neonatal tetanus is provided in Chapter 15.5. Almost similar principles apply for management of older children. The best survival rates with generalized tetanus are achieved with neuromuscular blocking agents like vecuronium and pancuronium. These drugs produce general flaccid paralysis, which can be managed by mechanical ventilation. Meticulous nursing care is imperative. The patient should be kept in a quiet, dark environment with minimum auditory or visual stimuli. Maintenance of nutrition, fluid and electrolyte balance, care suctioning of secretions and cardiorespiratory monitoring should be done. Provision for tracheostomy should be kept ready.

BOX 1 Differential diagnosis of tetanus

- Parapharyngeal, retropharyngeal or dental abscess—Trismus may be present
- Rabies—It may present with trismus and seizures but rabies is characterized by hydrophobia and aerophobia
- Viral encephalitis—It may present with tonic seizures but there is altered sensorium
- Hypocalcemia—It may produce tetani characterized by laryngeal and carpopedal spasms but trismus is absent.

PROGNOSIS

The average mortality of tetanus is 45–55%. For neonatal tetanus, the mortality is 60–70%. The most important factor influencing the outcome is supportive care. Recovery from tetanus does not confer immunity; therefore, active immunization of the patients following recovery is imperative.

PREVENTION

Tetanus is an entirely preventable disease. Active immunization is the best method to prevent tetanus. All children should be immunized with three doses of DPT at 6, 10 and 14 weeks followed by booster doses at 18 months and 5 years of age. Boosters should be given at 10 years and then every 10 years. Td or Tdap is the vaccine of choice above 7 years of age. Neonatal tetanus could be prevented by immunizing the pregnant women with two doses of tetanus toxoid (preferably Td) between 16 weeks and 36 weeks of pregnancy, and with only one dose of Td in the subsequent pregnancies.

Wound Management

All wounds should be cleaned, necrotic tissue and foreign material should be removed. Wounds, which are not minor, require human TIG except those in a fully immunized patient. In patients with unknown or incomplete immunization history, crush, puncture or projectile wounds, wounds contaminated with soil, saliva or feces, avulsion injuries, compound fractures, 250 U of TIG should be given IM. In cases where the wound could not be properly debrided or wound is more than 24 hours old, 500 U TIG should be given. Tetanus toxoid may be administered immediately depending on the previous immunization status of the child.

IN A NUTSHELL

1. Tetanus is an important preventable cause of neonatal death in developing countries.
2. Risk factors—Contamination of wound, unhygienic handling of the umbilical cord in newborns, lack of aseptic care during and after delivery
3. The spores germinate and produce tetanospasmin, a neurotoxin, which is responsible for the disease.
4. Difficulty in swallowing, restlessness, irritability and headache are early manifestations.
5. Laryngeal and respiratory muscle spasm can lead to airway obstruction and asphyxia.
6. Neonatal tetanus manifests within 3–12 days of birth.
7. Diagnosis is mainly clinical.
8. Human tetanus immunoglobulin (TIG) is recommended to be given immediately. Penicillin is the antibiotic of choice
9. The average mortality is 45–55%. For neonatal tetanus, the mortality is 60–70%.
10. Active immunization is the best method to prevent tetanus.

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Chapter 29.6

Typhoid Fever

Apurba Ghosh, Monjori Mitra

Typhoid fever is a systemic infection with protean manifestation caused by *Salmonella enterica* serotype Typhi (*S. typhi*). Today typhoid and paratyphoid fever remain an important public health problem, mostly involving children in the younger age group and young adults than in older patients.

EPIDEMIOLOGY

The estimated incidence in year 2000 was over 21.6 million episodes of typhoid worldwide, which resulted in death of nearly 2,16,000 patients. The incidence seems to be higher in South Central Asia and Southeast Asia (more than 100 cases per 1,00,000 person-years), because of the associated poor sanitation and unsafe food and water. Other regions of Asia and Africa, Latin America, the Caribbean, and Oceania have a medium incidence of 10–100 cases per 1,00,000 person-years. The burden of enteric fever is the least well characterized in sub-Saharan Africa. Antimicrobial resistance has emerged to traditional first-line drugs, fluoroquinolones and third-generation cephalosporins, creating treatment challenges adding to the concern. Hence, globally the focus remains in the prevention of this disease by improved sanitation and vaccine. Based on this global need, development of a better immunogenic conjugate typhoid vaccine has been developed and research is being undertaken to improve further.

ETIOLOGY

Typhoid fever is caused by *Salmonella* species, which are gram-negative bacilli and belong to the family Enterobacteriaceae. Serotyping is based on the identification of serogroup antigens, the flagellar (H) antigens, and the virulence (Vi) antigen. H antigens can be either phase 1 (nonspecific) or phase 2 (specific). Reactions of *Salmonella* with antisera to specific O (somatic) antigens determine the serogroups A, B, C1, C2, D, and E and further O, H (flagellar), and Vi (capsular) antigenic characterization results in a unique serotype that traditionally has served as a surrogate species designation, e.g., *S. typhi* (now recommended). In the current scenario *S. paratyphi* A was responsible for a growing proportion of enteric fever in a number of Asian countries, sometimes accounting for 50% of *Salmonella* bloodstream isolates among patients with enteric fever.

There are six subgroups of *Salmonella* based on deoxyribonucleic acid (DNA) hybridization and most of the serotypes which are important in human and animal disease, belong to subgroup I. The examples of serotypes are: A (*S. paratyphi* A), B (*S. typhimurium*, *S. heidelberg*, *S. paratyphi* B), C1 (*S. choleraesuis*, *S. infantis*), C2 (*S. newport*), and D (*S. enteritidis*, *S. typhi*). Nontyphoidal salmonellae have emerged as a major cause of bacteremia in Africa, especially among populations with high incidence of HIV infection. These are being dealt with in the next chapter.

Salmonellae are motile, nonsporulating, nonencapsulated, Gram-negative rods that grow aerobically and are capable of facultative anaerobic growth. They are resistant to refrigeration and sometimes heating but can be killed by heating to 130°F (54.4°C) for 1 hour or 140°F (60°C) for 15 min. They remain viable at ambient or reduced temperatures for days and may survive for weeks in sewage.

TRANSMISSION

Only humans are the carriers of *S. typhi*, which is present in the bloodstream and intestinal tract. *S. typhi* is transmitted mainly by feco-oral route and the bacilli get excreted for long duration in feces and urine of cases and carriers. It spreads through fecal contaminated drinking water or food and leads to large epidemics.

It can also be associated with poor standards of hygiene in food preparation and handling leading to direct transmission of infection. The hands may be contaminated while handling patients, their excreta or infected linen. Transmission by flies is also a possibility in endemic areas.

PATHOGENESIS

Severity of the disease and the incubation period depend on the size of the inoculum, host immunocompetence, prior antibiotic use and finally the DNA sequence of the *Salmonella* strain. In some outbreaks, very small inocula of *Salmonella* seem to have caused disease. Large inocula (e.g., 10⁹ organisms) may cause severe symptoms, even in healthy children. The incubation period usually is 6–72 hours but can extend up to 14 days.

The pathogenicity depends on the multiple factors, whereby the *Salmonella* strains can adhere to, invade and multiply in intestinal epithelium; produce cholera toxin-like enterotoxin that increases cyclic adenosine monophosphate levels within intestinal crypt cells, causing a net efflux of electrolytes and water into the intestinal lumen; be taken up by M cells overlying Peyer's patches of the distal ileum and proximal colon; survive in macrophages of Peyer's patches, mesenteric lymph nodes and the extraintestinal reticuloendothelial system (RES); and survive in the bloodstream. For each of these activities, the strain specific genes encode the virulence factors necessary for each step in these processes.

After ingestion, *S. typhi* organisms invade the body through the gut mucosa in the terminal ileum, through the specialized antigen-sampling cells known as *M cells* that overlie gut-associated lymphoid tissues, through enterocytes, or via a paracellular route. *S. typhi* crosses the intestinal mucosal barrier after attachment to the microvilli by an intricate mechanism involving membrane ruffling, actin rearrangement and internalization in an intracellular vacuole. Subsequently, they cause intestinal inflammation with polymorphonuclear leukocytes and macrophages involving the lamina propria. The underlying intestinal lymphoid tissue and mesenteric lymph nodes enlarge causing interference with the blood supply to the gut mucosa and may result in small areas of necrosis. Hyperplasia of the RES is also found within the liver and spleen. If bacteremia develops, it may lead to localized infection and suppuration in almost any organ. In contrast, the pathologic findings in *S. typhimurium* and other nontyphoidal serotypes cause diffuse colitis, mucosal edema and crypt abscesses. The invasiveness of the disease depends on the virulence factor of the various *Salmonella* genes, some are shared by all strains and some are serotype-specific. Virulence plasmids have been identified in *S. typhi*, *S. typhimurium* and *S. dublin*.

Salmonella pathogenicity islands (SPI) are an important virulence factor in vivo, in particular, SPI-1 and SPI-2. Both SPIs encode a molecular apparatus called type III secretion system, capable of injecting bacterial proteins through bacterial and host membranes into host cells (translocation) or the extracellular milieu (secretion) to influence host biochemistry and cell physiology directly.

Salmonella are able to survive in macrophages but not in polymorphonuclear leukocytes. Patients with neutropenia or neutrophil dysfunction are at high risk for development of disseminated infection. Cytokines play a crucial role in initiating and regulating the innate and adaptive immune response against

Salmonella. These bacteria can trigger synthesis of cytokines and chemokines in epithelial cells, macrophages and dendritic cells. The consequences of cytokine activation vary and at times with impaired immunity, there may be severe bacteremia following *Salmonella* infection.

Children with sickle-cell and S-Thal also sometimes develop osteomyelitis. Malaria predisposes to salmonellosis by multiple mechanisms. Schistosomiasis predisposes to development of *Salmonella* infections and prolonged bacteremia.

CLINICAL FEATURES

The mean age at onset of typhoid was 8.5 years for the site in Pakistan, 10.0 years in India, 10.2 years in Indonesia, 10.5 years in Vietnam and 12 years in China. The incubation period of typhoid fever is usually 4–14 days but depends on the infecting dose and ranges between 3 days and 30 days. The onset is insidious and varies from a mild illness with low-grade fever, malaise, and slight dry cough to a severe clinical picture with abdominal discomfort and multiple complications. The majority of patients with typhoid fever present with abdominal pain, fevers and chills. Children commonly complain of headache; they often are drowsy, irritable or delirious. Mild arthralgia involving multiple joints and vague, poorly localized back pain occur in nearly 60% of patients.

Classic reports described the characteristic stages of typhoid fever in untreated individuals. In the first week of illness, rising (*stepwise*) fever and bacteremia develop. While chills are typical, frank rigors are rare. Relative bradycardia or pulse-temperature dissociation may be observed. The patient has a dull, expressionless, toxic facies; coated tongue; a musty, *damp hay-like* odor; and a tender, doughy abdomen with slight guarding. Occasionally, a child may have a cough; it tends to be minimal and unimpressive. The skin is dry with little sweating. Meningismus may occur early in the illness.

In the 2nd week of illness, abdominal pain develops and *rose spots* (faint salmon-colored macules on the trunk and abdomen) may be seen. A soft, tender spleen is palpable, respiratory symptoms may progress, and epistaxis occasionally may occur. If untreated, typhoid fever has a prolonged course, with continuous high temperature of 39.5–40.5°C for up to 4 weeks, followed by a gradual return to normal, beginning during the 3rd or 4th week.

During the 3rd week of illness, hepatosplenomegaly, intestinal bleeding and perforation due to ileocecal lymphatic hyperplasia of the Peyer's patches may occur, together with secondary bacteremia and peritonitis. Septic shock or an altered level of consciousness may develop. In the absence of acute complications or death from overwhelming sepsis, symptoms gradually resolve over weeks to months.

Constipation occurs with approximately equal frequency but diarrhea may be more common, particularly in young children. When diarrhea develops, it usually does so after the patient has been febrile for several days. It is small in volume, resembles pea soup, and contains erythrocytes but usually is not grossly bloody. Fecal leukocytes are present in nearly all patients with diarrhea. Diarrhea occurs more commonly with paratyphoid than with typhoid fever.

Vomiting is mild and not sustained. Among 552 patients with culture-confirmed typhoid fever in Bangladesh, abdominal tenderness or distension (57%) and rectal bleeding (9%) were equally distributed across age groups. Headache is a frequent symptom reported in 44–94% of cases. Cough is not rare and has been observed in approximately 20–45%; arthralgia and myalgia occur in about 20%.

The clinical features of enteric fever in **Table 1** were observed in a study from India.

Table 1 Clinical features of enteric fever in India

Clinical findings	%
Fever > 38.4°C	100
Headache	67.8
Constipation/diarrhea	55.9
Poor appetite	35.7
Abdominal pain	63.3
Splenomegaly	24.7
Hepatomegaly	66.9

COMPLICATIONS

Complications occur in 10–15% of patients; most of these develop during the 2nd or 3rd week of illness. Although altered liver function is found in many patients with enteric fever, clinically significant hepatitis, jaundice and cholecystitis are relatively rare and may be associated with higher rates of adverse outcome. Intestinal perforation generally occurs more frequently among adults than children and is associated with high mortality rates.

Patients with severe typhoid fever may develop *typhoid encephalopathy*, with altered consciousness, delirium, and confusion, myelitis, acute cerebellar ataxia, chorea, deafness, and Guillain-Barré syndrome. Although case fatality rates may be higher with neurologic manifestations, recovery usually occurs with no sequelae. Other reported complications include fatal bone marrow necrosis, disseminated intravascular coagulation (DIC), hemolytic-uremic syndrome, pyelonephritis, nephrotic syndrome, meningitis, endocarditis, parotitis, orchitis and suppurative lymphadenitis.

Individuals who excrete *S. typhi* for more than or equal to 3 months after infection are regarded as chronic carriers. The risk for becoming a carrier is low in children (< 2% for all infected children) and increases with age. A chronic urinary carrier state can develop in children with schistosomiasis.

DIAGNOSIS

The mainstay of the diagnosis of typhoid fever is a positive result of blood culture. Blood cultures are positive in 40–80% of patients, depending upon the series and culture techniques used. The diagnosis can also be made by culture of stool, urine, rose spots, or duodenal contents (via string capsule). However, the sensitivity of blood cultures in diagnosing typhoid fever in many parts of the developing world is limited because widespread liberal antibiotic use may render bacteriologic confirmation difficult. Bone marrow cultures may be positive in as many as 50% of patients after as many as 5 days of antibiotics although bone marrow cultures may increase the likelihood of bacteriologic confirmation of typhoid, collection of the specimens is difficult and relatively invasive and hence not routinely practiced.

S. typhi isolates should be screened for resistance to nalidixic acid, or have formal sensitivity testing for the clinically used fluoroquinolones. Nalidixic acid resistant *Salmonella typhi* (NARST) should be anticipated to have reduced susceptibility to fluoroquinolones, even if the laboratory reports fluoroquinolone sensitivity.

Patients with typhoid fever frequently have anemia and either leukopenia or leukocytosis. Leukopenia with left shift is typically seen in adults while leukocytosis is more common in children. If observed in the 3rd week of illness, leukocytosis should prompt suspicion for intestinal perforation. Thrombocytopenia may be a marker of severe illness and may accompany DIC. Liver

function test results may be deranged, but significant hepatic dysfunction is rare. Cerebrospinal fluid studies are usually normal or reveal a mild pleocytosis (< 35 cells/mm³), even in patients with neuropsychiatric symptoms.

Serologic tests such as the Widal test are of limited clinical utility in endemic areas because positive results may represent previous infection. Positive results have been reported in 46–94% of cases. Because many false-positive and false-negative results occur, diagnosis of typhoid fever by Widal test alone is prone to error. Other relatively newer diagnostic tests using monoclonal antibodies have been developed that directly detect *S. typhi* specific antigens in the serum or *S. typhi* Vi antigen in the urine. A nested polymerase chain reaction analysis using *H1-d* primers has been used to amplify specific genes of *S. typhi* in the blood of patients; it is a promising means of making a rapid diagnosis, especially given the low level of bacteremia in enteric fever.

Newer serologic assays, Typhidot, using enzyme-linked immunosorbent assay (ELISA) and dipstick techniques perform somewhat better than the Widal test, but sensitivity and specificity are not adequate for routine diagnostic use. An ELISA for antibodies to the capsular polysaccharide Vi antigen is useful for detection of carriers, but not for the diagnosis of acute illness.

TREATMENT

With the emergence of multidrug resistance of *S. typhi* to the first-line drugs ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole in the 1990s, the treatment of typhoid was shifted to the quinolones and third generation cephalosporin. The intracellular site of *Salmonella* has favored the use of fluoroquinolones because of the theoretical advantage. In recent years, development of increasing resistance to fluoroquinolones has resulted in more challenges.

Resistance patterns have led to a shift toward the third generation cephalosporins, azithromycin and fluoroquinolones as empiric therapy for typhoid fever while awaiting the results of antimicrobial susceptibilities. With the development of fluoroquinolones resistance, third generation cephalosporins were used in treatment but sporadic reports of resistance to these antibiotics also followed. Recently, azithromycin is being used as an alternative agent for treatment of uncomplicated typhoid fever.

As per the guidelines developed by Indian Academy of Pediatrics for management of enteric fever, cefixime is the drug of choice for uncomplicated typhoid and third generation parenteral cephalosporins (ceftriaxone or cefotaxime) are drug of choice for severe typhoid. Aztreonam and imipenem may also be used as second line drugs (**Tables 2 and 3**). Fluoroquinolones can be used in life-threatening infections resistant to other recommended antibiotics.

Reports by elegant molecular studies have documented MDR clones of *S. typhi* in Africa and Asia that now account for many (85%–100% of outbreak strains in Kenya) isolates. These patterns of resistance appear to be shifting with changing pressures in antimicrobial use. Fluoroquinolone-resistant *S. paratyphi* A is an emerging problem in India and Nepal as fluoroquinolone use has flourished. Despite a steady rise in resistance in most studies, re-emergence of strains susceptible to first-line antimicrobial agents, including ampicillin, chloramphenicol and cotrimoxazole, has been reported.

Duration of therapy depends on serotype and site of infection. Ceftriaxone is the best initial parenteral choice because of widespread resistance to other agents. For susceptible strains, ampicillin, trimethoprim-sulfamethoxazole and chloramphenicol have all been used successfully, and fluoroquinolones have been used extensively, even in children in endemic areas.

Therapy usually is continued for 10–14 days in children, for 4–6 weeks for acute osteomyelitis and for 4 weeks for meningitis. In the developing world, *Salmonella* infection associated with schistosomiasis requires treatment of both infections to achieve resolution.

Defervescence in typhoid fever usually requires at least 36 hours of therapy and fever can persist for 5–7 days, even with ultimately effective therapy. Azithromycin has been effective in children with strains resistant to first-line agents.

Corticosteroids are used as adjunctive therapy in the presence of delirium, obtundation, stupor, coma, or shock in children with typhoid fever; a dose of 3 mg/kg dexamethasone initially, followed by 1 mg/kg every 6 hours for 48 hours, was associated with reduction of mortality from, between 35% and 55% to 10%. For patients in whom intestinal perforation develops, surgery coupled with broad-spectrum antimicrobial therapy directed at anaerobic and gram-negative enteric bacteria is indicated. The mortality after perforation can be as high as 10–30%.

Relapse

Relapse was considered with the recurrence of clinical disease, culture-proven infection with *Salmonella typhi* and *paratyphi* isolates (as described earlier), and with an antibiogram identical to the original isolates, within 8 weeks of cessation of successful therapy of the initial infection. **Table 4** depicts the rate of relapse in NARST infections. The relapse rate also varies with the antibiotic used for the initial treatment, though insufficient data, but it shows least rate of relapse with azithromycin and ofloxacin high dose.

The relapse rate is associated with various factors. Treatment of multidrug resistance (MDR) enteric fever with quinolones may be predicted to better eradicate *Salmonella* from the RES than treatment with first-line antimicrobials. Infection for greater than 14

Table 2 Treatment of uncomplicated typhoid fever

Susceptibility	First-line oral drug			Second-line oral drug		
	Antibiotic	Daily dose (mg/kg)	Days	Antibiotic	Daily dose (mg/kg)	Days
Fully sensitive	3rd gen. cephalosporin e.g., Cefixime	15–20	14	Chloramphenicol Amoxicillin Trimethoprim-Sulfamethoxazole (TMP-SMX)	50–75 75–100 8–TMP 40–SMX	14–21 14 14
Multidrug resistant	3rd gen. cephalosporin e.g., Cefixime	15–20	14	Azithromycin	10–20	7

Table 3 Treatment of severe typhoid

Susceptibility	First-line parenteral drug			Second-line parenteral drug		
	Antibiotic	Daily dose (mg/kg)	Days	Antibiotic	Daily dose (mg/kg)	Days
Fully sensitive	Ceftriaxone	50–75	14	Chloramphenicol	100	14–21
	Or			Ampicillin	100	14
	Cefotaxime			Trimethoprim-Sulfamethoxazole (TMP-SMX)	8-TMP 40-SMX	14
Multidrug resistant	Ceftriaxone	50–75	14	Aztreonam	50–100	14
	Or Cefotaxime					

Table 4 Rate of relapse in nalidixic acid resistant *Salmonella typhi* (NARST) infection

Drug	Dosage	Fever clearance time (Median or mean)	Rate of treatment failure	Relapse rate
Azithromycin	10–20 mg/kg od × 7d	4.4d	9%	< 1%; insufficient data
Cefixime	10 mg/kg bid × 7d	5.8d	27%	9%
Ceftriaxone	60–75 mg/kg qid × 10–14d	6.1d	9%	5%

days prior to therapy may lead to a greater immune system activation thereby allowing improved *Salmonella* clearance from the RES. Likewise, as this organism is shed through the stool, it is possible that constipation may lead to a higher load of organism within the body whereas diarrhea could be predicted to cause the opposite effect.

Despite appropriate therapy, 2–4% of infected children may experience relapse after initial clinical response to treatment. The same therapy should be repeated with proper dose and duration after sending culture. In case the empiric antibiotic is not sensitive, then it should be changed to appropriate sensitive antibiotic and the total duration should be based on the antibiotic type.

PREVENTION

The prevention of typhoid fever should focus on the control of the infection in the animal reservoir; prevent contaminated foods prepared from animals, and improvement in personal hygiene, sewerage and drinking water supply. Clean water supply, education in hand-washing, and food preparation and storage are critical to reducing person-to-person transmission. *Salmonella* may remain viable when cooking practices prevent food from reaching a temperature greater than 150°F (65.5°C) for more than 12 minutes.

Two safe and efficacious typhoid vaccines, the injectable Vi polysaccharide and the oral Ty21a, had been licensed but the oral vaccine due to its own limitation has not been used widely in the developing countries and is not available in India. Currently the new, improved typhoid conjugate vaccines are being tested and recently marketed in India. The Vi polysaccharide subunit vaccine was first licensed in the United States in 1994. It is composed of purified Vi capsular polysaccharide from the Ty2 *S. typhi* strain and elicits a T-cell-independent IgG response that is not boosted by additional doses. The vaccine is administered subcutaneously or intramuscularly. The Vi vaccine does not elicit adequate immune responses in children aged below 2 years. Several large field trials suggest that the Vi capsular vaccine as a single 25-μg dose (0.5 mL) has an efficacy of 55–75% in adults and children older than 5 years. Conjugate vaccines are also available now for those below 2 years of age. Detailed discussion on typhoid vaccines is available in Section 23.

IN A NUTSHELL

1. Typhoid fever is the commonest bacterial infection in the developing countries. In the developed countries, it is mostly because of the travelers.
2. The infection depends on the size of the inoculum, use of prior antibiotic, prevailing of the MDR strains and the DNA sequence of the organism.
3. There is an increasing surge of the paratyphi infection and is mostly because of the infection related to the poultry products.
4. The clinical features have an insidious onset with high rise of fever, headache, abdominal discomfort, both diarrhea and constipation and hepatosplenomegaly.
5. Complications of typhoid are seen in 10–15% with intestinal perforation and bleeding being the most serious in nature.
6. BACTEC culture positive is the gold standard ranging from 40–80% positivity. Serology though not specific but in late presentation can be an evidence of diagnosing with strong clinical suspicion, particularly with rising titer.
7. The first-line treatment for MDR typhoid is 3rd generation cephalosporins and quinolones, and the duration should be 14 days. But recently it has been seen that the quinolones are becoming resistant and the MIC of cephalosporin is increasing. Studies have shown azithromycin in the dose of 20 mg/kg for 5–7 days has a good efficacy.
8. Relapse of typhoid when occurs must be treated with the same drug as before unless the sensitivity report shows a different result and is continued for 14 days.
9. Prevention of typhoid has to be with improvement in the sanitation and good supply of drinking water.
10. Ultimately it has become a global concern to prevent typhoid by effective vaccine.

MORE ON THIS TOPIC

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Chapter 29.7

Nontyphoidal Salmonellosis

Thangavelu Sangaralingam, Janani Ravi

There are two forms of clinical expression of *Salmonella* infection: (1) Typhoid or paratyphoid fever caused by *Salmonella typhi* and *paratyphi*; and (2) *Salmonella enterocolitis* (including food poisoning) which may be complicated by bacteremia and/or focal suppurative complications, such as enteritis, cholecystitis, meningitis, arthritis, osteomyelitis, pneumonia and empyema. These organisms leading to the second presentation other than typhoid and paratyphoid are known as nontyphoidal salmonellosis. *S. enterica* is the new terminology and it has 2,500 serotypes. Among these, five serotypes are important (**Table 1**). *S. typhimurium* and *S. enteritidis* are most commonly incriminated in nontyphoidal salmonellosis.

EPIDEMIOLOGY

Nontyphoidal salmonellosis (NTS) is increasingly being reported in every country following consumption of common food preparations, such as animal products and eggs. The commonly affected age group is less than 5 years old with a peak between 6 months and 2 years. The disease is prevalent not only in humans but also in pet animals, livestock and poultry which act as reservoirs and continue to pose threat to humans. Studies on isolation of *Salmonella* from diarrhea stools in both humans and animals done in the Northeastern part of India showed that 14.4% of isolates in animals and 20% of stool samples in human beings isolated *Salmonella* serovars. Out of 13 million cases with nontyphoidal salmonellosis reported worldwide, about 70% are reported from three countries, India, China and Pakistan. The single largest reservoir of *Salmonella* is constituted by poultry. Many of the *Salmonella* strains are also developing resistance to common antimicrobials.

MICROBIOLOGY AND MODE OF SPREAD

Salmonella are gram-negative motile organisms with more than 2,500 serovars or serotypes. According to the current nomenclature, *S. enterica* is the common (single) name for all the medically important *Salmonella*. Three serotypes, namely *S. enteritidis* (39%), *S. typhimurium* (20%) and *S. newport* (9%) constitute more than half of the *Salmonella* infections isolated in humans in the United States. Prime reservoirs of NTS are poultry, livestock, reptiles and pets. The vehicles of transmission are food products of animal origin, like poultry, beef, eggs and dairy products. Other vehicles implicated are: vegetarian products contaminated with infected human or animal source, such as fruits, vegetables, peanut butter, frozen pot pies, powdered infant formulas, cereals and bakery products (**Table 2**). Predisposing factors for the development of salmonella infections are listed in **Table 3**.

Majority of nontyphoidal salmonellae are nonhost adapted (not host-specific) and hence have the potential to affect both human and animals. Three serovars, *S. typhi*, *S. typhimurium* and *S. paratyphi* play a prominent role in human infection.

CLINICAL FEATURES

Various clinical categories of *Salmonella* infections are acute gastroenteritis, bacteremia and focal infections (meningitis, pneumonia, arthritis, osteomyelitis, etc.). These are not discrete entities but form a clinical spectrum (**Table 4**).

Salmonella Gastroenteritis/Food Poisoning

The usual presentation is fever, nausea, headache, diarrhea with abdominal pain; *Salmonella* diarrhea cannot be clinically differentiated from other bacterial pathogens. Symptoms of food poisoning generally develop in 12–36 hours (range 6–72 hours) after the consumption depending on the amount of inoculum and host response. *Salmonella* gastroenteritis is a self-limiting illness: fever subsides by 48–72 hours and diarrhea resolves by 4–10 days. Most of the milder cases are not even recognized.

Salmonella Bacteremia

Bacteremia is a serious complication of *Salmonella* infection and believed to occur in 1–5% of the children with *Salmonella* diarrhea. Unlike in adults where 90% had underlying predisposing factors, majority of the children with *Salmonella* bacteremia were previously healthy. Organism and serotypes commonly involved are *S. enteritidis* and *S. typhimurium* and less commonly implicated serotypes are *dublin*, *choleraesuis*, *virchow*, *infantis* and *heidelberg*. The infection may spread to various organs resulting in arthritis, osteomyelitis, pneumonia, endocarditis, mycotic aneurysm and meningitis. Increased risk of bacteremia is associated with three species: *S. typhimurium*, *S. choleraesuis* and *S. heidelberg*.

Clinical Presentation

Predominant features of *Salmonella* bacteremia are fever, tachypnea and diarrhea. Out of 229 children with *Salmonella* bacteremia, 69% had respiratory symptoms and diarrhea. Pneumonia was present in 20.5% of the cases. As they fulfill the World Health Organization (WHO) criteria for pneumonia, there is a possibility of being treated for isolated pneumonia with penicillin and not with appropriate antibiotics for NTS. In children, 75% of the bacteremia were secondary to gastroenteritis and there was no death. However, in majority of the adults, bacteremia was primary and mortality was high amounting to 33%. In a retrospective study done in a pediatric hospital, 12 out of 144 children with bacteremia developed focal infection as complication.

Salmonella Meningitis

This is more commonly seen in neonates and infants, and more than three-fourths of the children affected were less than 1-year-old in most of the studies. *S. enteritidis* is the commonly incriminated organism reported and rarely *S. typhimurium*.

Table 1 Nomenclature for *Salmonella* organisms

Complete name	CDC designation	Commonly used name
<i>S. enterica</i> subspecies <i>enterica</i> serotype <i>typhi</i>	<i>S. ser. Typhi</i>	<i>S. typhi</i>
<i>S. enterica</i> subspecies <i>enterica</i> serotype <i>typhimurium</i>	<i>S. ser. Typhimurium</i>	<i>S. typhimurium</i>
<i>S. enterica</i> subspecies <i>enterica</i> serotype <i>newport</i>	<i>S. ser. Newport</i>	<i>S. newport</i>
<i>S. enterica</i> subspecies <i>enterica</i> serotype <i>choleraesuis</i>	<i>S. ser. Choleraesuis</i>	<i>S. choleraesuis</i>
<i>S. enterica</i> subspecies <i>enterica</i> serotype <i>enteritidis</i>	<i>S. ser. Enteritidis</i>	<i>S. enteritidis</i>

S. typhimurium will be called *Salmonella enterica*, serotype *Typhimurium*.

Table 2 Mode of infection of *Salmonella* infections

Mode of infection	Sources
Foodborne: animal origin	Undercooked eggs, or eggs showing no external evidence of infection or rotting, cheese, dry cereals, ice-cream premix
Other food vehicles	Fresh sprouts, peanut butter, frozen pot pies, juice, cantaloupes, bakery products, hot water-treated mangoes and fresh vegetables
Ingestion of contaminated water	Reptiles and birds
Contact with infected reptiles and amphibians	Pet turtles, lizards, snakes, frogs, toads, rodents
Nosocomial transmission	In the hospital from the affected child through stool or urine contamination; contaminated instruments, drugs and solutions

Table 3 Predisposing factors for GI salmonellosis and its sequelae

Factors	Affected population
Gastric hypoacidity	Infancy, use of H ₂ blockers and antacids
Extremes of age	
Alteration of endogenous flora	Antimicrobial therapy, surgery
Systemic diseases	Diabetes, rheumatological disorders, malignancy
Reticuloendothelial blockade	Sickle cell disease, malaria
Immunosuppression	HIV, immune deficiency, therapeutic immunosuppression, steroids
Anatomical disruption	Kidney stones, abnormalities of urinary tract, gall stones, prosthesis

Table 4 Clinical spectrum of *Salmonella* infection

Typhoid fever Caused by <i>S. typhi</i> or <i>paratyphi</i> A or B, this infection leads to systemic illness usually with little or no diarrhea. These organisms are highly adapted for humans. They do not cause colonization or disease in animals and are transmitted via fecal contaminated water or food items from an acutely affected human.
Nontyphoidal <i>Salmonella</i> This disease predominantly presents as diarrheal disease following consumption of food contaminated by animal or human fecal material. <i>S. typhimurium</i> and <i>enteritidis</i> cause gastroenteritis in children, but <i>S. choleraesuis</i> and <i>S. dublin</i> are associated with bacteremia and metastatic foci in humans. These organisms are nonadapted and hence cause diseases in human as well as animals.
• Enteritis
• Septicemia
• Localization: Meningitis, septic arthritis, osteomyelitis, cholangitis, pneumonia, endocarditis, mycotic aneurysm.

meningitis. These are rare causes of meningitis, constituting less than 1% of all causes of meningitis in neonates and infants. This is often associated with high mortality and morbidity. Both acute and chronic complications like neurodevelopmental sequelae, such as paralysis, deafness, seizures, visual disturbances and mental retardation are also more commonly encountered. Clinical presentation is similar to that of any other bacterial meningitis. It is more commonly suspected if the mother has suffered earlier from a salmonella infection and she remains as a carrier.

DIFFERENTIAL DIAGNOSIS

Escherichia coli, *Shigella*, *Campylobacter jejuni* and *Vibrio cholerae* are the common pathogens constituting bacterial etiology in acute diarrhea. Presence of blood in the stools usually favors the diagnosis of enterohemorrhagic *E. coli* or *Shigella*. In cases of suspected food poisoning, consumption of the food item is related to an individual or group of individuals, and time of onset of symptoms will be helpful to arrive at a diagnosis. In staphylococcal food poisoning, symptoms develop within 6 hours, but in *Salmonella*, the time gap will be a little later than 12–36 hours.

LABORATORY INVESTIGATIONS

In *Salmonella* gastroenteritis, stool microscopy may reveal the presence of pus cells. Fresh stools are ideal for culturing *Salmonella*. Stool culture is preferable in comparison with rectal swab because of higher specificity and sensitivity. Blood culture is positive if bacteremia is suspected. Other investigations such as imaging of bone or joint with bone scan are needed when child develops arthritis or osteomyelitis. MR imaging of the brain with CSF analysis is mandatory in salmonella meningitis.

Presence of neutrophils, low glucose and high protein in the cerebrospinal fluid (CSF) and additional presence of gram-negative bacilli is suggestive of *Salmonella* meningitis. Neuroimaging is a useful tool to identify the acute complications, such as subdural effusion, empyema, ventriculitis, hydrocephalus, abscess and intracranial hemorrhage. Blood, stool and urine culture may isolate *Salmonella* in cases with bacteremia.

MANAGEMENT

Salmonella Enterocolitis

Salmonella gastroenteritis is a self-limiting illness and the diarrhea is expected to be controlled within a period of 4–10 days. Management is mainly supportive using appropriate fluid and electrolyte therapy. Antibiotic therapy is not warranted in an uncomplicated child with *Salmonella* diarrhea and is rather supposed to prolong the duration of illness and fecal excretion rate. Hence, it is not recommended in general. However, the Center for Disease Control and Prevention (CDC) in the United States recommends antimicrobial therapy only for a selective category of children where there is increased risk of invasive infection—children younger than 3 months of age, those with chronic gastrointestinal disease, malignancy, hemoglobinopathies, HIV infection, immunosuppressive therapy or illnesses. Ampicillin, amoxicillin or co-trimoxazole is recommended in susceptible strains. In areas with high rate of antimicrobial resistance, third-generation cephalosporins and fluoroquinolones are the preferred choice. Duration of therapy is 5–7 days.

Salmonella Bacteremia

When *Salmonella* sepsis is suspected, infants less than 3 months and children with stool culture positivity should be hospitalized. Evaluation should be done to identify focal infections, like meningitis, osteomyelitis or arthritis. For invasive but nonfocal infection like bacteremia, usually the initial antibiotic is third-generation cephalosporin or quinolone for a period of 14 days. Most of the papers published prior to 2,000 showed poor outcome and high morbidity when these patients were treated with chloramphenicol and ampicillin. Availability of third-generation cephalosporins and fluoroquinolones has changed the outcome because of their higher efficacy.

Salmonella Meningitis

The ideal empirical antibiotic therapy in salmonella meningitis is ceftriaxone or cefotaxime alone or with a combination of third

generation along with quinolones. Alternative drugs in critically ill children are meropenem 120 mg/kg/day in 3 divided doses or cefepime 150 mg/kg/day in 3 divided doses, and later adjusted according to the sensitivity pattern. Generally, ceftriaxone is used for 4–6 weeks to complete the therapy. The commonly used empirical antibiotic combination in any young infant with meningitis, prior to microbiological diagnosis is ceftriaxone and gentamicin and will not be effective against *Salmonella* meningitis. Hence, a diagnosis of *Salmonella* meningitis should be suspected prior to obtaining cultures by the presence of gram-negative bacilli in the CSF by Gram stain, or culture growing gram-negative bacilli from any other specimen like blood or urine in a child with bacterial meningitis.

As per the British Society of Antimicrobial Therapy, duration of therapy should be for a minimum period of 3 weeks from the first sterile CSF, and CSF analysis should be done not earlier than 4 days of therapy. Recent reports indicate that ciprofloxacin causing arthropathy is extremely uncommon and the treatment of serious infection should definitely outweigh the risk. In neonates, cefotaxime is the right choice rather than ceftriaxone for the fear of bilirubin encephalopathy. When cefotaxime is used, it should be given in high doses of 200–300 mg/kg/day. The whole course should be given through intravenous route. As relapse is a potential problem, even after good clinical recovery, the child should be monitored vigilantly. At earliest evidence of relapse, the same drug combination can be restarted as the relapse is due to intracellular localization of the organism and insufficient penetration of the antibiotics. Of course, the duration of therapy will definitely have to be longer than the first therapy and should be modified by the clinical response in CSF.

PROGNOSIS

Prognosis is good in *Salmonella* gastroenteritis. In *Salmonella* bacteremia without focal complications, prognosis is good with antibiotic therapy for 10–14 days. Prognosis is guarded in focal infections. In *Salmonella* meningitis, the fatality rate, acute complication, relapse and later sequelae are high.

PREVENTION

As long as there is fecal or urinary excretion, there is a risk of transmission. In children younger than 5 years, 45% of them continue to excrete organisms in the feces even beyond 12 weeks, keeping the school or household contacts at risk. During this period, diaper and urine-soaked clothes should be properly

disposed. People handling food should be exempted from the work till they stop excretion of organisms. Eggs and other foods of animal origin should be cooked properly and raw egg or partially cooked egg consumption should be discouraged. Ultimately, proper hand hygiene is the best method that prevents transmission.

IN A NUTSHELL

1. Nontyphoidal salmonellosis is equally common like typhoid disease.
2. Suspect NTS when the child has features of enterocolitis without blood in the stools. Ordering for stool culture in appropriate circumstances will help in the diagnosis.
3. *Salmonella* bacteremia may resemble pneumonia. If atypical features like diarrhea, follow-up the blood culture for gram-negative bacilli.
4. Suspect NTS meningitis in early part of the disease when Gram stain showed gram-negative bacilli. It needs a broad coverage for longer period and careful monitoring for relapse.
5. Complications are more in *Salmonella* meningitis and need neuroimaging and early management of complication.
6. Prevention is possible with hygienic food handling and time-tested handwashing.

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Chapter 29.8

Haemophilus influenzae B Infections

Somu Sivabalan

Haemophilus influenzae is a pleomorphic gram-negative, facultative anaerobic coccobacillus that was first described during influenza pandemic by Richard Pfeiffer in 1892. Until 1933, this organism was mistakenly considered to be the cause of influenza till the viral etiology was identified. Yet in practice, the term *bacterial influenza* persists to exist. There are six identifiable typeable encapsulated (a, b, c, d, e and f) and nontypeable unencapsulated *Haemophilus influenzae* causing infections in children. The encapsulated serotypes have their distinct capsular polysaccharides. *Haemophilus* is responsible for a wide range of localized and invasive infections. *Haemophilus influenzae* type b (Hib) accounts for over 90% of serious infections with significant morbidity and mortality in infants and children younger than 5 years of age.

EPIDEMIOLOGY

In the year 2000, the World Health Organization (WHO) estimated that globally Hib caused over 8 million cases of serious disease and 376,000 deaths. Pneumonia and meningitis comprise the majority of the severe diseases caused by Hib in developing countries. Countries using Hib vaccine in national immunization programs have virtually eliminated Hib disease; however, Hib disease continues to occur in countries that do not use Hib vaccines widely. Studies have demonstrated a high burden of Hib disease in South and Southeast Asia.

It is believed and suggested that Hib disease is uncommon in Asia, largely due to unavailability of epidemiological data. In India, available data on Hib diseases indicates that Hib is one of the leading causes of meningitis and pneumonia in children less than 5-year-old. According to the WHO estimates, 2.4–3.0 million cases of Hib disease occur annually in the country with total deaths estimated to be at 72,000. During 1993–1997, a Prospective Surveillance Study and Review of acute Hib infections by Invasive Bacterial Infections Surveillance (IBIS) group of the International Clinical Epidemiology Network in 6 academic referral hospitals revealed significant disease burden, with substantial morbidity, mortality and drug resistance in children less than 5 years of age. This data also suggested universal immunization with available Hib vaccines will definitely benefit Indian children. Data revealed Hib contributes 40–50% of all meningitis and 25–30% of all pneumonia cases. Hib is the most common cause of meningitis and the second largest cause of pneumonia (after *Streptococcus pneumoniae*) in India. The case fatality ratio for the Hib meningitis and pneumonia is in the range of 10–30%. In addition to mortality, Hib causes a substantial morbidity burden with 25–30% of Hib meningitis survivors suffering from long-term neurological sequelae. It is estimated that mortality due to Hib disease contributes 4% of all annual under-5 deaths in India. The introduction of liquid pentavalent vaccine (LPV) in India having antigens of DPT, hepatitis B, and Hib is a major step forward to accelerate child survival in India.

TRANSMISSION

Hib spreads either by direct person to person contact or through respiratory droplets by coughing and sneezing. Most strains of *Haemophilus influenzae* bacteria, including Hib, are usual

commensals in upper respiratory flora and are harmless. They can cause noninvasive infection, like bronchitis, pneumonia or ear infection, by contiguous spread. In noninvasive form, disease is usually nonsevere and complications are rare with appropriate antibiotics. Sometimes, the bacteria can enter the blood and spread, causing serious invasive disease that can be serious or fatal. Most of the time, they are spread through asymptomatic people. The incubation period could be as short as a few days. The risk of transmission increases when children spend prolonged periods of time together in settings such as day-care or crèches. Children are often asymptomatic carriers of the Hib bacteria showing no signs or symptoms but still can infect others.

CLINICAL FEATURES

The most common manifestations of invasive *Haemophilus influenzae* disease are bacteremia (septicemia), meningitis, invasive pneumonia (through bloodstream), epiglottitis, cellulitis, infectious arthritis, and osteomyelitis or septic arthritis. Less common infections include endocarditis, endophthalmitis, peritonitis and gangrene. The disease occurs primarily in children aged less than 2 years, particularly in infants. Children between the ages of 4–18 months of age are most at risk. At birth, antibodies from the mother sufficiently protect most infants. When the child reaches 2 or 3 months of age, the level of maternal antibodies decreases and the risk of Hib infections increases. By the age 5 years, most children will have already developed their own immunity against Hib. Children with following medical conditions are at higher risk for developing a Hib infection: sickle cell disease; asplenia (no spleen); HIV infection; antibody and complement deficiency syndromes; and recipients of chemotherapy, radiation therapy for malignant neoplasms, and hematopoietic stem cell transplants.

COMPLICATIONS

Overall mortality from Hib meningitis is approximately 5%. Morbidity includes neurologic sequelae, like partial-to-total sensorineural hearing loss, developmental delay, language delay, behavioral abnormalities, language disorders, impaired vision, mental retardation, motor problems, ataxia, seizures and hydrocephalus. Approximately 6% of individuals with Hib meningitis experience permanent sensorineural hearing loss. Epiglottitis carries a mortality of 5–10% secondary to acute respiratory tract obstruction. Invasive neonatal disease carries a mortality rate of 55%.

DIAGNOSIS

The diagnosis of Hib disease can be made by bacterial culture, latex agglutination test or by polymerase chain reaction (PCR). It is very difficult to identify Hib in resource poor settings. The bacterial culture of CSF, blood, synovial, pleural, pericardial or peritoneal fluid is recommended. Gram stain of infected body fluids can facilitate presumptive diagnosis.

TREATMENT

Initial therapy for possible Hib meningitis and other invasive disease is either with intravenous *ceftriaxone* 100 mg/kg/24 hours OD/Q 12 hours. Max: 2 g/dose and 4 g/24 hours or *cefotaxime* 100–200 mg/kg/24 hours Q 6–8 hours IV. Meningitis dosage: 200 mg/kg/24 hours Q 6–8 hours. Max: 12 g/24 hours. *Ampicillin* (100–200 mg/kg/24 hours Q 6–8 h IV; severe infection 200–400 mg/kg IV every 4–6 hours, max 8 g/24 hours) could be used if isolate shows sensitive pattern. Therapy is at least for 10 days or longer in complicating infections. *Meropenem* (120 mg/kg/24 hours or 40 mg/kg IV Q 8 hours IV, max 6 g/24 hours) is an alternate empiric agent in drug resistant cases. *Dexamethasone* (0.4 mg/kg Q 12 hours IV for 2 days or 0.15 mg/kg Q 6 hours for 4 days) is beneficial in diminishing the risk of hearing loss

if given before or concurrently with the first dose of antimicrobials. In epiglottitis, airway should be secured by endotracheal tube or tracheostomy in addition to antimicrobials. In infected pleural or pericardial collections, the fluid should be drained. Treatment is not always effective because some strains may be resistant to antibiotics. Isolates produce beta-lactamase necessitating beta-lactamase resistant agent. Antibiotic resistance is a serious problem, which is continuously increasing in developing countries, including India.

CONTROL MEASURES

These are measures undertaken to control the risk and spread of Hib infection. These include: (1) Isolation of index case patients with invasive Hib disease: droplet precautions are recommended for 24 hours after initiation of effective antimicrobial therapy; (2) care of the exposed people: careful observation of exposed, unimmunized or incompletely immunized children who are in household, child care or nursery school contact of patients with invasive Hib disease is essential (**Flow chart 1**). Exposed children in whom febrile illness develops should receive prompt medical evaluation. Household contact is defined as people who reside with the index patient or nonresidents who spent 4 or more hours with the index patient for at least 5 of the 7 days preceding the day of hospital admission of the index case; (3) chemoprophylaxis when necessary and (4) routine Hib immunization of the community.

Chemoprophylaxis

Rifampicin eradicates Hib from the pharynx in approximately 95% of carriers and decreases the risk of secondary invasive illness in household contacts. The risk of invasive disease is increased among unimmunized household contacts younger than 4 years of age; secondary disease in child care contacts is rare when contacts are older than 2 years of age. Treatment of index case with ceftriaxone or cefotaxime eradicates Hib colonization, eliminating the need

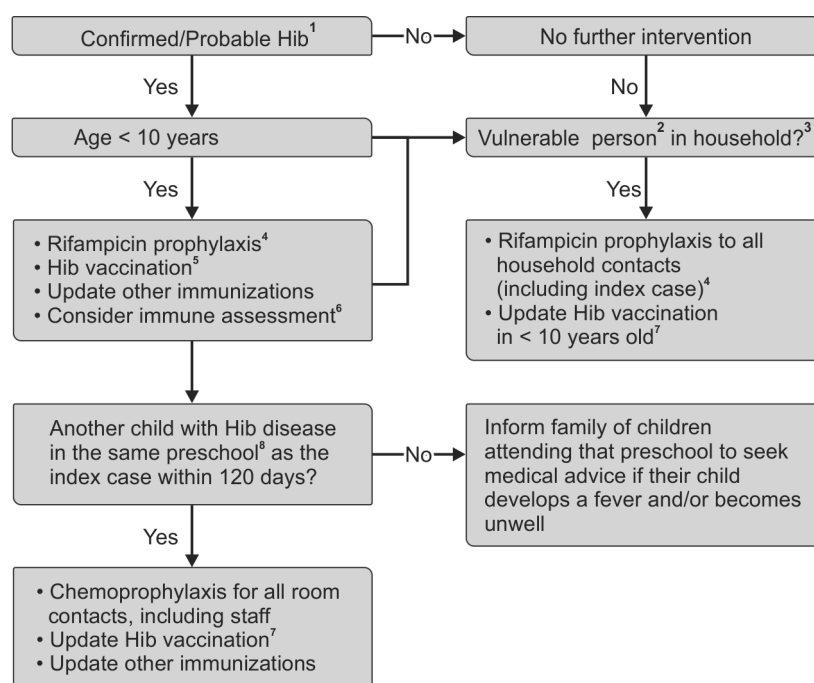
for prophylaxis, whereas those treated with other antimicrobials and who are younger than 2 years of age should receive rifampicin prophylaxis at the end of therapy.

Hib Vaccine

Hib containing vaccines provide 85–95% protection after completion of the schedule. In addition to the effects directly attributed to the vaccine, they reduce nasopharyngeal colonization and carriage of the organism, leading to substantially greater reduction in disease transmission and incidence than can be directly attributed to the effects of the vaccine. This indirect effect or *herd immunity* and reductions in antibiotic resistance by preventing disease and appropriate use of antibiotics have been demonstrated in several postintroduction effectiveness studies. All Hib vaccines are conjugated vaccines where the Hib capsular polysaccharide (polyribosylribitol phosphate or PRP) is conjugated with a protein carrier so as to provide protection in the early years of life when it is most needed. The vaccination schedule for Hib consists of three doses when initiated below 6 months, 2 doses between 6 and 12 months and 1 dose between 12 and 15 months, with a booster at 18 months. For children aged more than 15 months, a single dose may suffice. The interval between two doses should be at least 4 weeks. Immunization can be commenced as early as 6 weeks of age. Details on Hib vaccine are given in Section 23 on immunization.

More than 170 countries now include Hib vaccine in their national immunization program. By contrast, introduction of the vaccine in India has been delayed. In 2008, India's National Technical Advisory Group on immunization recommended inclusion of Hib vaccine into the universal immunization program (UIP). Based on this recommendation, the Government of India recently decided to introduce Hib-containing pentavalent vaccine into the UIP of 10 Indian states.

Flow chart 1 Guidelines for the management of close contacts of Hib. Open access document from: Revised recommendations for the prevention of secondary *Haemophilus influenzae* type b (Hib) disease (Updated 1 July, 2013) by Department of health and Public health England—NHS England. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/231009/Revised_recommendations_for_the_preventions_of_secondary_Haemophilus_influenzae_type_b_disease.pdf. Accessed April 16, 2014.



EMERGING TRENDS

The spectacular progress in developed countries in preventing Hib infections by universal vaccination over the past 2 decades has resulted in changes in colonization and epidemiology of invasive *H. influenzae* disease. There has been an observed shift from predominantly serotype b strains to predominantly nontypeable strains. There is no convincing evidence of an increased incidence of invasive disease by nonserotype b strains of *H. influenzae*, i.e., no strain replacement. However, this issue requires continued vigilant surveillance.

IN A NUTSHELL

1. Globally, every year, Hib kills more than 370,000 children under 5 years of age. Nearly 20% of these children are from India.
2. The most common manifestations of invasive *Haemophilus influenzae* disease are bacteremia, meningitis, invasive pneumonia, epiglottitis, cellulitis, infectious arthritis, and osteomyelitis or septic arthritis. Less common infections include endocarditis, endophthalmitis, peritonitis and gangrene.
3. The disease occurs primarily in children aged less than 2 years, particularly in infants. Children between the ages of 4–18 months of age are most at risk.
4. Hib spreads either by direct person to person contact or through respiratory droplets.
5. Dexamethasone is beneficial in diminishing the risk of hearing loss if given before or concurrently with the first dose of antimicrobials.
6. Rifampicin eradicates Hib from the pharynx in approximately 95% of carriers and decreases the risk of secondary invasive illness in household contacts.
7. Hib vaccine can prevent over one-third of pneumonia cases and 90% of Hib meningitis cases.

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Chapter 29.9

Pneumococcal Infections

Meenu Singh, Nishant Jaiswal

Pneumococcal disease is the term used to describe infections caused by the bacterium *Streptococcus pneumoniae* (also called *pneumococcus*). Pasteur first isolated the bacterium in 1881 from the saliva of a patient with rabies. Friedlander and Talamon first described the association between the *Pneumococcus* bacterium and lobar pneumonia in 1883, but pneumococcal pneumonia was confused with other types of pneumonia until the discovery of the Gram stain in 1884. By 1940, more than 80 serotypes were known. Efforts to develop effective pneumococcal vaccines began as early as 1911. However, with the advent of penicillin in the 1940s, interest in the vaccine declined, until it was observed that many patients still died despite antibiotic treatment. By the late 1960s, efforts were again being made to develop a polyvalent pneumococcal vaccine. The first pneumococcal vaccine was licensed in the United States in 1977. The first conjugate pneumococcal vaccine was licensed in 2000.

MORPHOLOGY AND VIRULENCE

S. pneumoniae are lancet-shaped, gram-positive, catalase-negative facultative anaerobic organisms. They are typically observed in pairs (diplococci) but may also occur singularly or in short chains. *S. pneumoniae* may or may not be capsulated. Encapsulated strains are pathogenic for humans and other animals, whereas the uncapsulated forms are nonpathogenic. The capsule is the most important virulence factor. Over 90 different capsular serotypes have been characterized.

S. pneumoniae belong to the α -hemolytic group that characteristically produces a greenish color on blood agar because of the reduction of iron in hemoglobin. The bacteria are fastidious and grow best in 5% CO₂ but require a source of catalase (e.g., blood) for growth on agar plates, where they develop mucoid (smooth/shiny) colonies. Pneumococci without a capsule produce colonies with a rough surface. Unlike that of other hemolytic streptococci, their growth is inhibited in the presence of optochin (ethyl hydrocuprein hydrochloride), and they are bile soluble.

Most *S. pneumoniae* serotypes have been shown to cause serious disease, but only a few serotypes produce the majority of pneumococcal infections. The ranking and serotype prevalence differ by patient age group and geographic area. Some serotypes of the *Pneumococcus* may be carried in the nasopharynx without symptoms, with disease occurring in a small proportion of infected individuals. Other serotypes are rarely identified in the nasopharynx but are associated with invasive disease. The incubation period for pneumococcal disease is not clearly defined but it may be as short as one to three days. The organism may spread locally into the sinuses or middle ear cavity, causing sinusitis or otitis media. It may also affect the lungs to cause pneumonia, or cause systemic (invasive) infections including bacteremia and meningitis.

PATHOGENESIS

Pneumococci colonize the human nasopharynx from an early age. Colonization acquisition events are generally described as asymptomatic, but evidence exists to associate acquisition with mild respiratory symptoms, especially in the very young. From the nasopharynx, the bacteria spread either via the bloodstream to distant sites (e.g., brain, joint, bones, peritoneal cavity) or locally to mucosal surfaces where they can cause otitis media or pneumonia. Direct spread from the nasopharynx to the central nervous system

(CNS) can occur in rare cases of skull base fracture, although most cases of pneumococcal meningitis are secondary to hematogenous spread. Pneumococci can cause disease in almost any organ or part of the body; however, otitis media, pneumonia, bacteremia and meningitis are most common.

Pneumococcal diseases occur throughout the world and infect both extremes of life (children under 5 years and elderly). It also affects those with an absent or nonfunctioning spleen and those with other causes of impaired immunity. *Pneumococcus* can cause meningitis and severe pneumonia, leading to an estimated 14.5 million cases of serious illness and 735,000 deaths each year in HIV-negative children under 5 years of age. National estimates of deaths due to *Pneumococcus* among children under 5 years of age ranged from 141,000 in India to fewer than 10 deaths in 46 countries. Nineteen percent of all pneumococcal deaths below 5 years of age occurred in India. Six countries (India, Nigeria, Ethiopia, DR Congo, Afghanistan and China) accounted for more than half of all pneumococcal deaths under age five in 2000.

TRANSMISSION

Pneumococcus resides in the nasopharynx of the asymptomatic human carriers and has no animal or insect vector. It spreads via direct person-to-person contact by respiratory droplet or autoinoculation. Overcrowding, seasonal variation, unhygienic conditions and presence of upper respiratory tract infection or other noninvasive pneumococcal diseases facilitate the spread.

Risk Factors

Lack of exclusive breastfeeding, nutritional deficiencies and indoor air pollution are risk factors for pneumonia, including pneumococcal pneumonia in infants and young children. Asplenic children (both functional and anatomical) particularly with sickle cell disease and immunocompromised children (particularly with HIV infection) are even at a higher risk for invasive disease. Moreover, children living in overcrowded, unhygienic areas and those attending childcare centers have shown more predispositions for invasive pneumococcal disease.

CLINICAL FEATURES

S. pneumoniae causes conjunctivitis, otitis media, sinusitis and pneumonia by direct invasion from the nasopharynx as well as meningitis and bacteremia by invasion and hematogenous spread.

Conjunctivitis

S. pneumoniae is the second most common cause of bacterial conjunctivitis in children; it is a more common cause of epidemic outbreaks among young adults. Acute bacterial conjunctivitis presents typically with burning, irritation, tearing and purulent or mucopurulent discharge. Conjunctival swelling and mild edema of the eyelid may occur as well.

Otitis Media

The most common bacterial pathogen causing otitis media in children and adults is *S. pneumoniae*. It commonly occurs after a viral infection that leads to eustachian tube congestion. It usually presents with a rapid onset of signs and symptoms such as otalgia, irritability in an infant or toddler, otorrhea and/or fever. Complications of acute otitis media include mild conductive hearing loss, vestibular balance dysfunction, tympanic membrane perforation, mastoiditis, petrositis and labyrinthitis. Rarely, intracranial complications may occur, which include meningitis, epidural abscess, brain abscess, lateral venous sinus thrombosis, cavernous sinus thrombosis, subdural empyema and carotid artery thrombosis.

Sinusitis

S. pneumoniae commonly affects the maxillary and the ethmoid sinuses. It is usually preceded by a viral infection, leading to mucosal swelling of the sinuses and obstruction of the ostia. This leads to the development of a purulent discharge and cough. Postnasal drip resulting in malodorous breath and worsening cough during night may also occur. Infection may extend into the cranium, leading to cavernous sinus thrombosis; brain, epidural or subdural abscesses or meningitis.

Pneumonia

Pneumococcal pneumonia is one of the most frequent serious bacterial infections. It may manifest as lobar pneumonia or, less commonly, as bronchopneumonia. It is also a common cause of bacterial community acquired pneumonia in HIV-infected patients. The incubation period of pneumococcal pneumonia lasts only about 1–3 days. Symptoms include an abrupt onset of fever with chills or rigors, pleuritic chest pain, productive cough with mucopurulent and rusty sputum, dyspnea, tachypnea, hypoxia, tachycardia, malaise, weakness and fatigue. Nausea, vomiting and headaches occur less frequently. Complications of pneumococcal pneumonia include pleural effusion, empyema, pericarditis and respiratory failure.

Meningitis

Pneumococcus causes acute purulent meningitis that may be secondary to bacteremia from other foci like pneumonia, direct extension from the infection of the ear, mastoid process or paranasal sinuses, or basilar fracture of the skull or cribriform plate [leading to cerebrospinal fluid (CSF) leakage]. This provides the bacteria residing in paranasal sinuses, nasopharynx or middle ear with access to the CNS.

The presenting signs and symptoms may be nonspecific that include fever, irritability, vomiting, lethargy, anorexia and malaise. Neurologic signs and symptoms include mental status changes, delirium, lethargy, nuchal rigidity, seizures, cranial nerve palsies and other focal neurological deficits. Infants may have a bulging fontanel and poor feeding, whereas elderly patients present with more indolent signs, such as increasing lethargy, nonresponsiveness or coma. Complications of pneumococcal meningitis include hearing loss, seizures, learning disabilities, mental dysfunction and cranial nerve palsies.

Bacteremia

The most common manifestation of invasive pneumococcal disease is bacteremia. It can occur in both immunocompetent and immunosuppressed patients with particular risk in patients who have undergone a splenectomy. Children less than 2 years of age are the most affected. Generally, the presentation is nonspecific. In most patients, high-grade fever develops within 24 hours of positive culture findings, and there is presence of a peripheral WBC count greater than 15,000 cells/ μ L. Complications include meningitis, osteomyelitis, pneumonia, endocarditis, soft tissue and joint infections, and sepsis.

DIAGNOSIS

The laboratory diagnosis in suspected pneumococcal infection includes Gram stain and culture of blood, CSF, sputum, pleural fluid or lung aspirate, joint fluid, bone or other tissue specimens. *Pneumococcus* typically appears as lancet-shaped diplococci on Gram stain. The characteristic capsule can be detected using the Quellung test or by staining using methylene blue. Culture confirms identification and antimicrobial susceptibility testing is

also performed routinely. For epidemiologic purposes, serotyping and genotyping of isolates may also be performed.

TREATMENT

The initial empiric antibiotic therapy pending antibiotic susceptibility tests is determined by local resistance patterns. Penicillin is the drug of first choice. Penicillin and its derivatives can be used for treating susceptible pneumococcal infections. The mechanism of action of penicillins is by inhibition of cell wall synthesis. These can be administered orally or parenterally. The usual doses of penicillin provide adequate serum and body fluid concentrations for susceptible organisms. The coverage of first-generation cephalosporins is similar to penicillin-susceptible strains. Macrolides usually are active against penicillin-susceptible strains of *S. pneumoniae*. Their CSF penetration is poor and, thus, should not be used to treat meningitis. Vancomycin, a glycopeptide antibiotic is the drug of choice (along with third-generation cephalosporins) against pneumococcal meningitis.

Carbapenems are also effective broad-spectrum antibiotics but should be reserved for specific cases due to potential for development of resistance to multiple organisms. β -lactams or macrolides are generally preferred but treatment has become more challenging as resistant strains have emerged worldwide. The rapid development and spread of antibiotic resistance has occurred due to multiple factors, of which prior antibiotic use, young age and day-care attendance are the predominant risk factors.

The method of resistance of pneumococci varies greatly for different antibiotics. Resistance to penicillins is mediated by alterations in the cell wall penicillin-binding proteins, cephalosporins, sulfonamides, trimethoprim-sulfamethoxazole by amino acid changes, macrolides by methylation or efflux pump, quinolones by decreased permeability, efflux pumps, and alteration of enzymes and chloramphenicol by inactivating enzymes. Resistance to multiple antibiotics is obtained by a bacterium by a transposon or is encoded in a cassette containing genetic information.

Due to increasing resistance of pneumococcal isolates to trimethoprim-sulfamethoxazole, it is not preferred unless drug susceptibilities are known and use of beta-lactams is contraindicated.

Specific Therapy

The first-line treatment for *acute otitis media* and *sinusitis* is amoxicillin 80–90 mg/kg/day. If no improvement is observed within 48–72 hours, patients should be re-evaluated and switched to amoxicillin-clavulanate or a second- or third-generation oral cephalosporin. If the pneumococci are highly resistant, they may require treatment with parenteral ceftriaxone to achieve adequate serum levels of antibiotics.

For mild-to-moderate bacterial *community acquired pneumonia*, the first-line therapy is amoxicillin (90 mg/kg/day in two doses or 45 mg/kg/day in three doses) for previously healthy infants, preschool and school-aged children, and adolescents. In children older than 5 years, macrolides are added for coverage of atypical organisms. In hospitalized previously healthy children and adolescents, ampicillin or penicillin G is the recommended first-line treatment. In critically ill or immunocompromised children, empiric therapy should include vancomycin and a broad-spectrum cephalosporin until antibiotic susceptibilities are available.

The empiric therapy for meningitis consists of vancomycin and cefotaxime or ceftriaxone at meningeal doses. Antibiotics should be changed accordingly when antibiotic susceptibility test results are available.

PREVENTION

Vaccines

Two vaccines are available against *S. pneumoniae*: a pneumococcal conjugate vaccine (PCV13/PCV10) and a polyvalent polysaccharide vaccine (PPV23). Conjugated vaccine is recommended for all children aged 6 weeks to 59 months. The schedule varies according to age and underlying medical conditions. Children who begin vaccination at age less than or equal to 6 months, three-dose primary series is given beginning at about 2 months at every 2-month interval, followed by a fourth dose at age 12–15 months of age. For children who begin vaccination at 7–11 months of age, a two-dose primary series and a booster are given. From age 12 to 23 months, only 2 doses are given. From 24 months to 9 years of age, children are given only one dose of the vaccine. Adults, who are immunocompromised, have functional or anatomic asplenia, CSF leaks or cochlear implants and are not previously vaccinated with PPV23 should receive a dose of PCV13 first, followed by a dose of PPV23 at least after 8 weeks.

Polysaccharide vaccine is ineffective in children less than 2 years of age but causes reduction by 50% for invasive pneumococcal infection and bacteremia. It provides protection lasting for many years, but one-time revaccination is recommended after more than or equal to 5 years for patients with functional or anatomic asplenia and immunocompromised patients. It is usually indicated for adults more than or equal to 65 years and before splenectomy. It is not recommended for children less than 2 years or in those who are hypersensitive to the vaccine's components.

Prophylactic Antibiotics

Prophylactic penicillin V 125 mg per oral twice a day is recommended for children with functional or anatomic asplenia who are less than 5 years of age. The duration for chemoprophylaxis is variable, but it is usually continued throughout childhood and into adulthood for high-risk patients with asplenia. Penicillin 250 mg per oral twice a day is recommended for older children or adolescents for at least 1 year after splenectomy.

IN A NUTSHELL

1. *Pneumococcus* is gram-positive lancet-shaped catalase-negative facultative anaerobic diplococci. Encapsulated forms are virulent and over 90 serotypes are known based on the capsule.
2. *Pneumococcus* resides in the nasopharynx of the asymptomatic human carriers and has no animal or insect vector and spreads via direct person-to-person contact by droplet spread or direct inoculation.
3. *Pneumococcus* causes both invasive and noninvasive diseases, like otitis media, community acquired pneumonia and meningitis, etc.
4. Amoxicillin is the drug of choice for otitis media and community acquired pneumonia, and vancomycin along with cefotaxime are the drug of choice for pneumococcal meningitis.
5. Pneumococcal conjugate vaccines are used to immunize children less than 2 years of age against *pneumococcus*. Pneumococcal polysaccharide vaccine is recommended for elderly, before splenectomy and a revaccination with PPSV is indicated for patients more than 5 years of age with functional or anatomical asplenia.

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Chapter 29.10

Streptococcal Infections

Pramod Sharma

Streptococcus is a large group of nonmotile, nonspore forming, catalase and oxidase negative, spherical gram-positive cocci arranged in chains. They are part of the normal flora of humans and animals. Some of them are human pathogens and may be responsible for a wide range of invasive and noninvasive infections. The name is derived from the Greek word *streptos* meaning twisted chains; under a microscope, they resemble a string of small pearls.

CLASSIFICATION

Streptococci are divided into obligate anaerobes and facultative organisms. The former are designated peptostreptococci and are beyond the scope of this chapter. The aerobic and facultative anaerobes are classified based on their hemolytic properties. Brown (1919) categorized them into three varieties based on their growth in horse blood agar culture plates.

1. *Alpha-hemolytic Streptococci* cause partial hemolysis and a greenish discoloration. Hence, they are called *Streptococcus viridians* (viridians-green). These are normal commensals but may cause opportunistic infections at times.
2. *Beta-hemolytic Streptococci* Most pathogenic Streptococci belong to this group.
3. *Gamma streptococci* Include the fecal Streptococci (*Streptococcus faecalis*) or enterococci.

Lancefield Grouping

Hemolytic Streptococci were classified serologically into groups based on nature of a carbohydrate (C) antigen on the cell wall. Majority of organisms producing human infections belong to Group A. Group A β -hemolytic streptococci (GAS) are known as *Streptococcus pyogenes*. Lancefield grouping of other hemolytic Streptococci is shown in **Table 1**. GAS are further divided into types based on the protein antigens (M, T and R) present on the cell surface (*Griffith typing*). More than 20 types of GAS have been identified on the basis of M protein (located on cell surface and fimbriae) antigen typing. M protein sequence typing, using polymerase chain reaction is based on sequencing the *emm* gene, encoding the M protein. Chromosomal arrangements of *emm* subfamily genes reveal 5 major patterns of *emm*: Pattern A to E.

GROUP A STREPTOCOCCAL INFECTIONS

S. pyogenes It causes suppurative infections chiefly of upper respiratory tract (pharyngitis) and skin, viz., impetigo and pyoderma. GAS also causes scarlet fever, erysipelas, necrotizing fasciitis, and toxic shock syndrome (TSS). It is less commonly implicated in cellulitis, vaginitis, pneumonia, endocarditis,

pericarditis, osteomyelitis, omphalitis and suppurative arthritis. GAS triggers two nonsuppurative postinfectious complications: acute glomerulonephritis and acute rheumatic fever (ARF).

Epidemiology

Streptococcal pharyngitis is highly communicable and usually results from contact with respiratory tract secretions of an infected person. It affects all age groups but is more common in school-aged group (5–15 years). The disease is more common during winter, late autumn and spring season and in temperate climates. Communicability is highest during acute infection and from untreated persons. Patients are not contagious within 24 hours of initiation of appropriate antibiotics.

Impetigo (pyoderma) is more common in tropical climates and warm seasons and spreads by direct contact. GAS invades open skin lesions, viz., insect bites, burns, traumatic wounds, etc. Infections of surgical wounds and puerperal sepsis are usually transmitted by hands, anal and vaginal carriers. Neonatal infections can result from intrapartum or contact transmission which present as cellulitis, omphalitis or necrotizing fasciitis.

Invasive GAS infections occur mostly in infants and older age group. Varicella has been identified as the most common risk factor. Other risk factors include HIV infection, intravenous drug use, diabetes mellitus and chronic cardiac and pulmonary disease. The entry site is believed to be skin or mucous membrane though in 50% cases, the portal of entry is not known.

Pathogenesis

The major surface protein of GAS is M protein. The presence of M protein on a GAS isolate correlates with its capacity to resist phagocytic killing and improves adherence. This resistance is overcome by M protein-specific antibodies. GAS elaborates other antigens and enzymes responsible for virulence of different subtypes. The polysaccharide capsule protects from lysozymal defense of hosts. Streptokinase digests clots, hyaluronidase digests binding substance in connective tissues, DNases digest DNA, streptolysins S and O cause hemolysis and damage cell membranes and tissues, pyrogenic toxin—key toxin for rash of scarlet fever, affects temperature regulating center and C5a protease hinders complement and neutrophilic response.

Clinical Manifestations

Incubation period is 2–5 days for pharyngitis, and 7–10 days for impetigo.

Pharyngitis

Acute pharyngotonsillitis is the most common GAS infection and symptoms include sore throat, fever with chills, malaise and abdominal discomfort and vomiting. Exudative pharyngitis is commonly accompanied by enlarged, tender anterior cervical lymph nodes, fever and purulent exudates over the posterior pharyngeal wall (*Centor criteria*). Serous rhinitis, moderate fever, irritability, anorexia and lymphadenopathy may be seen

Table 1 Lancefield grouping of other hemolytic Streptococci

Species	Hemolytic group	Lancefield group	Diseases
<i>Streptococcus agalactiae</i> (GBS)	Beta	B	Neonatal meningitis, septicemia
Enterococci (<i>S. faecalis</i>)	Gamma	D	Endocarditis, UTI, rarely suppurative infections
<i>S. bovis</i> (Nonenterococci)	Gamma	D	Endocarditis, bacteremia
Viridans (<i>S. sanguis</i>)	Alpha	—	Endocarditis, dental caries (<i>S. mutans</i>), brain abscess

in toddlers. Classic Streptococcal pharyngitis is rare in children younger than 3 years.

Impetigo

Skin is the second most common site of GAS infection. The usual sites of involvement are face (around nose and mouth) and legs. Lesions start as red papules which quickly evolve into painless vesicular and pustular lesions that break down and coalesce to form honeycomb-like crusts.

Scarlet Fever

Uncommon in Indian population, it is characterized by confluent erythematous, finely papular sandpaper-like rash which blanches on pressure. It is caused by pyrogenic exotoxin. Rash appears within 24–48 hours of symptoms. It begins around neck and spreads to trunk and extremities with circumoral pallor. Tongue is usually coated and has swollen papillae which on desquamation becomes reddened and gives a *strawberry* appearance.

Necrotizing Fasciitis

This is also called Streptococcal gangrene. It is an acute rapidly progressive, severe deep-seated infection of the subcutaneous tissue associated with extensive destruction of the superficial and deep fascia. It may arise following minor trauma or from hematogenous spread of GAS from the throat to the site of a blunt trauma or muscular strain.

Invasive Group A β -hemolytic Streptococci Infections

Invasive GAS infections can be associated with *Streptococcal* TSS. Ability of certain Streptococcal pyogenic exotoxins to function as superantigen leads to a triggered hyperimmune response. This severe disease is characterized by shock, multiple organ dysfunction syndrome (MODS) and hematological and neurological anomalies.

Group A β -hemolytic Streptococci infections are seldom associated with sudden onset of obsessive compulsive disorder or tic disorder, which has been described as pediatric autoimmune neuropsychiatric disorders associated with *S. pyogenes* (PANDAS).

DIAGNOSIS

Laboratory confirmation of GAS infection is confirmed by culture on sheep blood agar. Differentiation of group A from other beta-hemolytic Streptococci is done by latex agglutination, coagglutination, fluorescent antibody or precipitation techniques performed on the grown colonies. An adequate specimen is taken by vigorous swabbing of both tonsils and posterior pharynx. A single culture has a sensitivity of 90–95% for detecting the presence of GAS in the pharynx. Other rapid diagnostic tests are mostly based on nitrous acid extraction of group A carbohydrate antigen from cultured organisms. These rapid diagnostic tests are >95% specific. Commercially available slide agglutination (streptozyme) test detects antibodies to several Streptococcal antigens. Discs containing 0.04 U of bacitracin inhibits the growth of > 95% of group A strains while 80–90% of nongroup A are resistant to this antibiotic.

TREATMENT

Pharyngitis

Penicillin V is the drug of choice of GAS pharyngitis. In children allergic to penicillin, erythromycin, clarithromycin or azithromycin is used. Amoxicillin is a good alternative and can be given once daily in a dose of 50 mg/kg for 10 days. A 10-day course of a narrow spectrum oral cephalosporin is recommended for most penicillin allergic children.

Impetigo

Local application of mupirocin ointment helps preventing person-to-person spread and eradicating localized disease. Systemic antimicrobials are indicated in multiple lesions and impetigo in family.

Parenteral antimicrobials are required in severe infections (meningitis, sepsis, pneumonia, endocarditis, septic arthritis, necrotizing fasciitis, osteomyelitis, surgical wound infection, neonatal omphalitis and Streptococcal shock syndrome). The treatment of various Streptococcal infections is shown in **Table 2**.

Table 2 Treatment of Streptococcal infection

Infection	Treatment
Pharyngitis	Penicillin V 250 mg PO tid or 500 mg PO bid \times 10 days Or erythromycin, oral cephalosporin, azithromycin Benzathine penicillin G (children <27 kg—600,000 IU IM, children >27 kg—1,200,000 IU IM \times 10 days)
Impetigo	Same as pharyngitis
Erysipelas/cellulitis	Severe: Penicillin G 1–2 mU IV q4h Mild to moderate: Procaine penicillin 1–2 mU IM bid
Necrotizing fasciitis/myositis	Surgical debridement; plus penicillin G 2–4 mU IV q4h; plus clindamycin 600–900 mg q8h
Pneumonia/empyema	Penicillin G 2–4 mU IV q4h; plus drainage of empyema
Streptococcal toxic shock syndrome	Penicillin G 2–4 mU IV q4h; plus clindamycin 600–900 mg q8h; plus intravenous immunoglobulin, 2 g/kg single dose

NONSUPPURATIVE SEQUELAE OF STREPTOCOCCAL INFECTIONS

Poststreptococcal Acute Glomerulonephritis

Glomerulonephritis can follow GAS infection of either the pharynx or the skin and depends on the prevalence of nephritogenic strain of GAS in the community. M serotype 12 is most frequently associated with poststreptococcal acute glomerulonephritis after pharyngitis and M type 49 is the serotype most commonly related to pyoderma-associated nephritis. Other strains implicated are M types 4 and 25. In most cases, there is a history of sore throat or pyoderma, latent period being 7–14 days in former and 2–4 weeks in later. The pathogenesis appears to be immune-mediated. Immunoglobulins, complement components and antigens that react with Streptococci are present in the glomeruli early in the course of the disease and antibodies elicited by nephritogenic Streptococci react with renal tissues to propagate glomerular injury. Immune complexes may be in circulation or formed in situ. Diagnosis is based on an evidence of recent Streptococcal infection: Antistreptolysin O (ASO) titers are raised in blood and C3 levels and CH 50 levels are decreased. Clinical course and management issues are discussed in Section 41 on kidney diseases.

Acute Rheumatic Fever

Acute rheumatic fever is delayed nonsuppurative sequelae of acute tonsillopharyngitis caused by GAS. There is usually a latent period of 2–3 weeks between pharyngitis and rheumatic fever. Not all serotypes of group A *Streptococcus* are associated with rheumatic fever. There are certain serotypes (M type 1, 3, 5, 6, 18, 24) which are commonly isolated from patients of rheumatic fever. Streptococcal

antigenic components (M protein, cell membrane, cell wall group A carbohydrate, capsular hyaluronate) mimic normal human tissue antigens (heart, brain, joint) leading to abnormal humoral and cellular immune responses (*molecular mimicry*). Rheumatic valves display increased expression of vascular cell adhesion molecule 1 (VCAM-1) a protein that mediates the adhesion of lymphocytes. Rate of development of rheumatic fever in children with untreated Streptococcal infection is estimated to be 3%. Incidence of recurrence with a subsequent untreated infection is about 50%.

Another theory is cytotoxic theory according to which rheumatic fever is caused by several cytotoxic enzymes produced by group A *Streptococcus*, but this theory fails to explain latent period between pharyngitis and rheumatic fever. Upcoming evidence supports the role of host susceptibility and genetic predisposition in rheumatic fever and components of MHC Class II—the DR 7 allele on chromosome 6 is associated with *RHD*. Detailed description of ARF follows in Section 40 on cardiovascular diseases.

Supporting evidence of recent Streptococcal infection is essential for the diagnosis of rheumatic fever. Only 10–20% of throat culture or rapid Streptococcal antigen tests are positive. Evidence of recent infection is thus based on elevated or rising serum antistreptococcal antibody titer. Raised ASO is seen in 80–85% cases and 95–100% patients of ARF can be diagnosed if three different antibody titers are measured (*ASO*, *anti-DNase B* and *hyaluronidase*).

GROUP B STREPTOCOCCAL INFECTIONS

Group B streptococci (GBS) or *S. agalactiae* are gram-positive diplococci which are classified into nine serotypes on the basis of capsular polysaccharides. Serotype III is the most common pathogen for early onset meningitis and most late onset infections in infants. GBS commonly colonize gastrointestinal and genitourinary tracts. Maximum colonizing rate (15–40%) is observed in pregnant women and newborn infants. GBS can be acquired in nursery from hospital personnel by hand contamination. The risk of early onset neonatal infection (0–6 days) increases with prematurity, prolonged rupture of membranes (> 18 hours), chorioamnionitis, GBS bacteriuria during pregnancy, intrapartum fever more than or equal to 38°C ($\geq 100.4^{\circ}\text{F}$) or previous infant with invasive GBS disease. Late onset disease (7 days–3 months) manifests as occult bacteremia or meningitis.

Other focal infections are osteomyelitis, adenitis, septic arthritis and cellulitis. Ampicillin plus an aminoglycoside (gentamicin) are initial treatment of choice. Infants with bacteremia or soft tissue infection should receive penicillin in a dosage of 200,000 U/kg/day in divided doses and in cases of meningitis should receive 400,000 U/kg/day. In meningitis, 14-day course should be given to prevent relapses.

IN A NUTSHELL

1. Streptococci are classified as alpha-hemolytic (*S. viridans*), beta-hemolytic (Group A: *S. pyogenes*; Group B: *S. agalactiae*) and gamma-hemolytic (*S. fecalis*).
2. *S. pyogenes* causes pharyngitis, impetigo and pyoderma. GAS also cause scarlet fever, erysipelas, necrotizing fasciitis, and TSS. They are also implicated in cellulitis, vaginitis, pneumonia, endocarditis, pericarditis, osteomyelitis, omphalitis and suppurative arthritis. GAS triggers two nonsuppurative postinfectious complications: acute glomerulonephritis and ARF.
3. Group B streptococci or *S. agalactiae* commonly colonize gastrointestinal and genitourinary tracts. These result in early onset sepsis and meningitis in newborn infants in the western world. These organisms are less common in Indian settings.

MORE ON THIS TOPIC

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Chapter 29.11

Staphylococcal Infections

Zaki Syed

Staphylococci are ubiquitous in nature and can survive as both commensals and pathogens. They are aerobic or facultative anaerobic, nonmotile, nonsporulating, gram-positive cocci that grow in pairs and clusters which resemble grapes (*staphylo* in Greek means *bunch of grapes*). They belong to the family *Staphylococcaceae* and can survive for long on environmental surfaces in varying conditions. They are catalase-positive unlike streptococcal species. The genus *Staphylococcus* consists of more than 30 distinct species. **Flow chart 1** shows the classification of the clinically important species depending on the biochemical tests.

Two species are commonly associated with Staphylococcal disease in humans: *S. aureus* and *S. epidermidis*. *S. aureus* causes infections ranging from trivial skin infection to lethal invasive disease. In comparison, *S. epidermidis* is less virulent and invasive except in an immunocompromised host or in the presence of an indwelling foreign body (e.g., catheter).

EPIDEMIOLOGY

Staphylococci cause millions of community-acquired and health-care associated infections in the developing world each year. About 50–60% of these infections are caused by methicillin-resistant *S. aureus* (MRSA). MRSA has now become endemic in India with incidence varying from 25% to 50%. Before mid-1990s, MRSA strains were exclusively hospital-associated, but recently their prevalence has increased in the community too. The community-acquired MRSA strains have the ability to cause serious infections even in immunocompetent individuals which is a cause for concern.

About 50% of healthy individuals may be persistently or temporarily colonized with *Staphylococci* in sites like the nose, skin, hairs, nails, axillae and perineum. The rate of colonization is comparatively much higher in immunosuppressed individuals. Asymptomatic carriers are at increased risk of infection for themselves and others. Other routes of transmission include: contact with infected persons, airborne spread and contact with contaminated objects. *Staphylococci* are widespread in the environment and can be cultured from virtually all known surfaces. Airborne transmission can occur in health facilities having operating rooms with poor ventilation. *S. aureus* is a common cause for nosocomial infections. Transient colonization of the hands of hospital personnel can result in transmission of infection amongst patients. This can be minimized by effective handwashing. In addition, hospital personnel with mild or inapparent lesions, such as stye, furuncle or paronychia should be adequately treated to limit spread. *Coagulase-negative staphylococci* (CoNS) commonly inhabit skin and mucus membrane of normal humans. The widespread use of invasive therapeutic modalities (e.g., mechanical ventilation, central venous catheters) has increased the incidence of infection from CoNS.

PATHOGENESIS

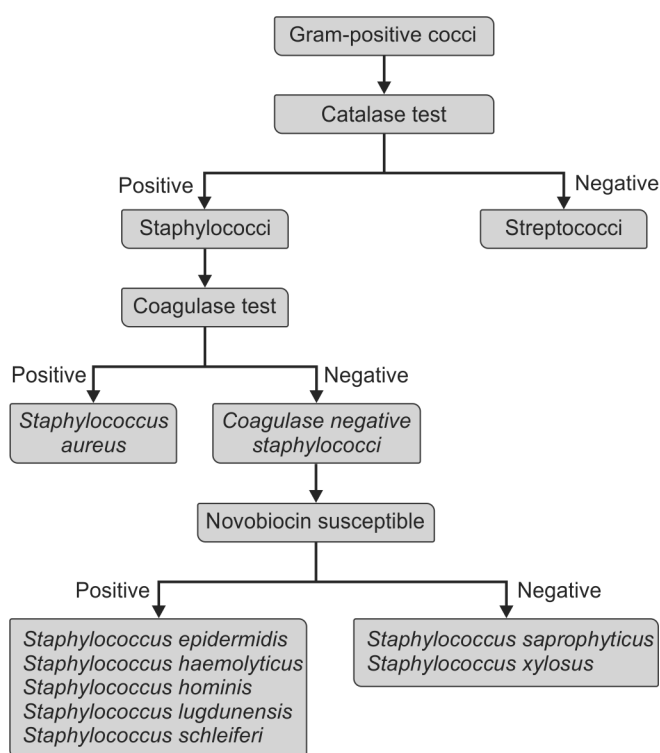
Virulence Factors

Staphylococci can colonize the skin, invade blood stream, evade host immunological responses, form protective biofilms and develop resistance to several antibiotics. The virulence factors of *Staphylococci* are shown in **Box 1**. They have the ability to produce a biofilm, or slime layer around itself. This biofilm enhances the adhesion of the organism to foreign surfaces, resists phagocytosis by macrophages and decreases the penetration of antimicrobial agents. **Table 1** compares the virulence factors of *S. aureus* and *S. epidermidis*.

Mechanism of Disease

Staphylococci cause disease by two mechanisms: tissue invasion and toxin-mediated. The host defense consists of an intact skin barrier and innate immune system. Conditions where the skin barrier is breached (e.g., burns, chronic skin disease, skin abrasions, and surgical procedures), increases the risk of Staphylococcal infections. The second defense is the host's innate immune system wherein the *Staphylococci* are killed by the neutrophils at the infection site. However, *Staphylococci* produce various virulence factors that can block each step of this host response. The presence of large numbers of organisms can overwhelm the host innate-immune response resulting in the spread of infection. Congenital/acquired neutrophil disorders (e.g., Jobs syndrome) increase the risk of Staphylococcal infection. *S. saprophyticus* can adhere to uroepithelial cells and result in urinary tract infection in patients with urinary catheters in situ. Toxin-mediated diseases of *Staphylococci* are: food poisoning, toxic shock syndrome (TSS) and Staphylococcal-scalded skin syndrome. Staphylococcal food poisoning is caused by a preformed heat-stable enterotoxin. TSS is caused by toxic shock syndrome toxin-1 (TSST-1), or other Staphylococcal enterotoxins, which act as superantigens. These bind to major histocompatibility complex class II molecules of antigen presenting cells. This binding stimulates the release of several cytokines from T-cells causing septic shock and death. The exfoliative toxins, A or B, secreted by the *S. aureus* can cause Staphylococcal-scalded skin syndrome. These toxins are proteases that specifically cleave desmoglein 1 (a desmosomal protein) that attaches the superficial epidermis to the underlying stratum granulosum.

Flow chart 1 Classification of clinically important Staphylococcal species



BOX 1 List of various virulence factors of *Staphylococci* with their pathogenetic mechanism*Thwart host defenses*

- Microcapsule
- Protein A
- Coagulase
- Slime layer
- Fatty acid metabolizing enzyme
- Leukocidin

Invade tissue

- Proteases
- Nucleases
- Lipases
- Hyaluronidase
- Staphylokinase

Resistance determinants

- *SCCmec* type IV: Resistance to methicillin
- *SCC₄₇₆*: Resistance to fusidic acid

Elicit sepsis syndrome

- Toxic shock syndrome toxin
- Enterotoxins (A, B, C, G, H, L, and O)
- Cytolytic toxins (a, b, g, and d)
- Exfoliative toxin (A and B)

Pore-forming toxins

- Panton-Valentine leukocidin (PVL) (*LukSPV+LukPFV*): Necrosis, edema
- LukE+LukD: Destruction of intestinal microvilli causes postantibiotic diarrhea
- LukEv+LukDv: Necrosis
- α -hemolysin: Necrosis, vascular leakage, and shock

Attach to endothelial cells and basement membrane

- Binding proteins for fibrinogen, fibronectin, laminin, collagen, vitronectin, and thrombospondin.

Table 1 Comparison of the virulence factors of *Staphylococcal* species

Virulence factor	<i>S. aureus</i>	<i>S. epidermidis</i>
Protein A	+	–
Coagulase	+	–
Catalase	+	+
Hyaluronidase	+	–
Staphylokinase	+	–
Lipase	+	+
Beta-lactamase	+	–

CLINICAL FEATURES***Staphylococcus aureus* Infections**

The symptomatology varies depending upon the site of infection.

Skin and Soft Tissue Infections

S. aureus commonly causes skin and soft tissue infections. These include impetigo, folliculitis, hydradenitis, furuncle, pyomyositis, carbuncle, abscess, erysipelas, cellulitis, necrotizing fasciitis and Staphylococcal scalded skin syndrome. Predisposing factors include: skin diseases, skin damage (e.g., trauma) and poor personal hygiene. *Staphylococcus* can also cause nosocomial skin infections. Community-associated MRSA can cause recurrent skin and soft tissue abscesses.

Bacteremia and Sepsis

Staphylococcal bacteremia and sepsis can be either primary or secondary to any localized infections. Organisms can localize

subsequently at any site, e.g., heart valves, lungs, joints, kidneys and bones. The clinical presentation of *S. aureus* sepsis is similar to sepsis due to other bacteria. Congenital/acquired immunosuppression predisposes to Staphylococcal bacteremia. In Staphylococcal bacteremia, the possibility of endocarditis, osteomyelitis or other metastatic deep infection must be considered.

Bones and Joints

S. aureus can cause acute/chronic osteomyelitis and septic arthritis through hematogenous seeding, trauma or surgical procedure. Long bones are commonly affected. The commonly affected joints are the wrist, hip, knee and ankle joints. Treatment includes antimicrobial therapy and drainage of the infected joint by needle aspiration, arthrotomy, or arthroscopically.

Respiratory Tract

S. aureus can rarely cause upper respiratory tract infections, otitis media, suppurative parotitis and sinusitis. Staphylococcal sinusitis and pneumonia are common in cystic fibrosis. Tracheitis complicating viral croup can develop due to *S. aureus*. Patients present with high fever, leukocytosis, severe obstruction of upper airway, or a shock-like picture. Treatment requires antibiotics and careful airway management. *S. aureus* can cause pneumonia by two ways: primary through hematogenous spread; secondary after a viral infection (e.g., influenza). *S. aureus* can cause necrotizing pneumonitis, interstitial pneumonia, empyema, lung abscess, pneumatocoeles, pyopneumothorax and bronchopleural fistula. *S. aureus* and MRSA in particular can cause hospital-acquired and ventilator-associated pneumonia with a high mortality. The diagnosis is done by examination of Gram stain of tracheal aspirate, sputum or lavage which shows the organism and several neutrophils. The culture is highly sensitive but less specific.

Central Nervous System

Community-acquired meningitis due to *S. aureus* is uncommon. Predisposing factors include: surgical procedures (e.g., shunt insertion, craniotomy), head trauma, endocarditis, epidural or brain abscess, cavernous sinus thrombosis and immunosuppression. Mortality is high ranging from 30% to 50%. The CSF profile of *S. aureus* meningitis is similar to other bacterial causes of meningitis.

Heart

Staphylococcal bacteremia may cause infective endocarditis even on native valves. Perforation of valves, heart failure, conduction disturbance, myocardial abscess, acute hemopericardium, purulent pericarditis and sudden death may occur.

Kidney

S. aureus can occasionally cause renal/perinephric abscess and urinary tract infection by hematogenous spread. Instrumentation of the genitourinary tract can result in ascending infections.

Prosthetic Device-related Infections

S. aureus can cause infection of various prosthetic devices like prosthetic valves, peritoneal/intraventricular catheters, intravascular catheters and vascular grafts. CoNS infections of prosthetic devices have a more indolent presentation as compared to *S. aureus* device-related infections which presents acutely and progresses rapidly with both localized and systemic manifestations. Treatment is antibiotic therapy and removal of the device.

Toxin-mediated Disease

Food poisoning The source can be an infected or colonized food handler. It has a short incubation period and the patient presents

within 2–6 hours with nausea, vomiting, abdominal pain and diarrhea. Fever is absent and the illness is self-limiting. Treatment is entirely supportive.

Toxic shock syndrome The causes of TSS are shown in **Box 2**. The disease starts abruptly with high fever, diarrhea, vomiting, headache and myalgia. A diffuse erythematous macular rash appears within 24 hours. The diagnostic criteria are shown in **Box 3**. Complications include acute respiratory distress syndrome, myocardial dysfunction, and renal failure. Recovery occurs within 7–10 days and is associated with desquamation, particularly of palms and soles. Blood cultures are usually negative. Removal of the source of infection (tampons, nasal packs), parenteral administration of a beta-lactamase resistant antibiotic (nafcillin or a first generation cephalosporin) for methicillin-susceptible, penicillinase-resistant *S. aureus* (MSSA) or vancomycin for MRSA strains along with aggressive supportive treatment is recommended. Clindamycin may be added in severe cases to terminate toxin production. Even with treatment, the overall mortality rate is 3%.

BOX 2 Risk factors of Staphylococcal toxic shock syndrome

- Menstruating women using tampons
- Use of vaginal devices (diaphragm, contraceptive sponge)
- Vaginal—postpartum or following infection
- Surgical wounds like hernia, mastoplasty and arthroscopy
- Respiratory tract infections (sinusitis, tracheitis, pneumonia, empyema)
- Abscesses, burns
- Osteomyelitis
- Varicella infection
- Nasal packing.

BOX 3 Diagnostic criteria of Staphylococcal toxic shock syndrome developed by the Centers for Disease Control and Prevention

Major criteria: All four should be present:

1. **Fever:** Temperature $>38.9^{\circ}\text{C}$
2. **Rash:** Diffuse macular erythroderma on the trunk
3. **Desquamation:** 1–2 weeks after onset, mainly of palms and soles
4. **Hypotension:** Systolic blood pressure <90 mmHg for adults and $<5^{\text{th}}$ centile for age for children <16 years of age or orthostatic syncope

Minor criteria: Three or more should be present:

1. **Gastrointestinal:** Vomiting and/or diarrhea at the onset of illness
2. **Muscular:** Severe myalgia or creatine kinase $>$ twice upper limit of normal
3. **Mucus membrane:** Hyperemia of the vaginal, oropharyngeal or conjunctival mucosa
4. **Renal dysfunction:** Blood urea nitrogen or creatinine level at least twice upper limit of normal, or > 5 white blood cells per high power field in urine in the absence of urinary tract infection
5. **Liver dysfunction:** Total bilirubin, aspartate aminotransferase or alanine transferase at least twice upper limit of normal
6. **Thrombocytopenia:** Platelet count < 1 lac/cumm
7. **Central nervous system:** Altered consciousness without focal neurological signs in the absence of fever and hypotension

Exclusion criteria: Normal results on the following tests (if performed):

1. Negative blood, throat or cerebrospinal fluid cultures (except occasionally for *S. aureus*)
2. Absence of another explanation.

Staphylococcal-scalded skin syndrome The disease commonly affects infants but can occasionally be seen in adults too. The illness varies from localized blister formation to exfoliation of much of the skin surface. The mucus membranes are usually spared. Constitutional symptoms like lethargy, fever, irritability and poor feeding are present in more generalized infection.

Infections with Coagulase Negative *Staphylococcus*

As CoNS are less virulent, they cause clinical disease usually in an immunocompromised host or in the presence of a foreign body in situ. CoNS can cause bacteremia and endocarditis in patients with catheter or shunt in situ. It can also cause shunt and catheter infections. CoNS bacteremia is indolent and usually does not progress to septic shock. Central venous catheter infection presents with fever, leukocytosis, tenderness and erythema at the exit site or along the subcutaneous tunnel. Most shunt infections due to CoNS occur within 2 months of the operation. Clinically, it presents with meningeal signs and peritonitis due to the intra-abdominal position of the distal end of the shunt tubing.

DIAGNOSIS

Staphylococcus aureus

The gold standard for diagnosis of *S. aureus* infection is isolation of the organism in cultures of blood, tissue or pus. Gram stain can provide a provisional diagnosis of Staphylococcal infection. The specificity of isolating *S. aureus* from blood or other sterile body sites is 100%. Isolation of *S. aureus* from culture of a respiratory specimen lacks specificity because of nasopharyngeal colonization in some uninfected individuals. Serologic assays are not useful. Susceptibility testing should be performed to guide antimicrobial therapy. Also, it will determine sensitivity of the isolate to methicillin. Diagnosis of Staphylococcal food poisoning is made on epidemiologic and clinical findings. Culture of the contaminated food should be done and tested for enterotoxin.

Coagulase-negative *Staphylococcus*

S. epidermidis is a common skin inhabitant and can contaminate inappropriately collected blood cultures. Hence, differentiating true bacteremia from contamination becomes difficult. True bacteremia is more likely if: there is rapid growth of blood cultures (within 24 hours); more than or equal to two blood cultures are positive with same CoNS; the peripheral venous blood culture has a quantitative colony count comparable to that drawn from central venous catheter; and clinical symptomatology and laboratory findings compatible with CoNS sepsis are present which resolve after therapy.

MANAGEMENT

Staphylococcus aureus

All suppurative collections should be relieved by incision and drainage. In prosthetic-device infections, the device should be removed. If removal is impossible or the infection is due to CoNS, an initial attempt at medical therapy should be tried. Treatment should be started with an antibiotic depending upon the severity of infection and the Staphylococcal susceptibility pattern of the area. Penicillin or amoxicillin should not be used, as more than 90% of all Staphylococcal isolates are penicillin-resistant. Quinolones are not recommended for use in serious infections due to low cure rates. The indications for antimicrobial therapy are shown in **Box 4**.

Skin and soft tissue infections can be usually managed by oral antibiotics and drainage. Oral dicloxacillin, cephalexin, amoxicillin-clavulanate, trimethoprim-sulfamethoxazole or doxycycline is effective for MSSA. Patients with hypersensitivity to penicillin can be treated with clindamycin for skin, soft tissue, bone and joint infections.

Parenteral treatment should be started in serious infections till the patient has been afebrile for 72 hours and signs of infection have decreased. Then oral therapy is given for at least 3 weeks or longer depending on the clinical response, radiological and laboratory findings. The drugs used for treatment of serious

BOX 4 Indications for antibiotic therapy in Staphylococcal infection

- Infections like cellulitis and pneumonia
- Infection where drainage is impossible or inadequate
- Presence of systemic signs and symptoms
- Invasive disease, i.e., secondary sites of infection, involvement of deep tissues, vital organs and sterile sites
- Bacteremia.

infections are shown in **Table 2**. Rifampin or gentamicin may be added for synergy. After starting the treatment, improvement in the general condition of the patient (e.g., toxicity, feeding and activity) should be monitored.

Vancomycin Resistance

Three types of Staphylococcal resistance to vancomycin have emerged recently:

1. *Vancomycin-intermediate S. aureus* (VISA) [minimum inhibitory concentration (MIC) 4–8 mcg/mL] Reduced

susceptibility in these strains is due to the synthesis of an unusually thickened cell wall containing dipeptides reducing availability of the drug for intracellular target molecules.

2. *Heterogeneous vancomycin-intermediate S. aureus* (hVISA) These are VISA strains in which subpopulations display variable rather than uniform susceptibility to vancomycin.
3. *High-level vancomycin-resistant S. aureus* (VRSA) (MIC ≥ 16 mcg/mL) The mechanism is plasmid-mediated transfer of the *vanA* gene cluster from enterococci with vancomycin resistance (via mobile genetic elements).

The optimal antimicrobial regimen for VRSA strains is unknown. Alternatives to vancomycin include quinupristin-dalfopristin, linezolid, daptomycin and telavancin.

Coagulase-negative Staphylococcus

Most CoNS strains are methicillin-resistant and the drug of choice for treatment is vancomycin. Rifampin or gentamicin can be added to increase the antimicrobial efficacy. The infected catheter or shunt should be removed for complete cure.

Table 2 Recommended antimicrobial agents used in the parenteral treatment of serious *S. aureus* infection

I. Initial empirical treatment when susceptibility of organism is unknown		
Drug of choice	Vancomycin + nafcillin or oxacillin \pm gentamicin	For life-threatening infections (i.e., septicemia, endocarditis, CNS infection)
	Nafcillin or oxacillin	For nonlife-threatening, community-acquired infection (e.g., skin infection, cellulitis, osteomyelitis, pyarthrosis) when prevalence of MRSA is low
	Clindamycin	For nonlife-threatening, community-acquired infection when prevalence of MRSA is high
	*Vancomycin	For nonlife-threatening, hospital-acquired infections
II. Treatment of methicillin-susceptible, penicillinase-resistant <i>S. aureus</i> (MSSA)		
Drug of choice	Nafcillin or oxacillin	–
Alternatives	<ul style="list-style-type: none"> • Cefazolin • Clindamycin • Ampicillin + sulbactam 	–
	*Vancomycin	For penicillin and cephalosporin allergic patients
III. Treatment of methicillin-resistant <i>S. aureus</i> (MRSA)		
A. Hospital associated (multidrug resistant)		
Drug of choice	Vancomycin \pm gentamicin or \pm rifampin	
Alternatives: Sensitivity test should be done before using these drugs.	<ul style="list-style-type: none"> • Trimethoprim-sulfamethoxazole • Linezolid • Quinupristin-dalfopristin 	
B. Treatment of community-acquired MRSA (not multidrug-resistant)		
Drug of choice	Vancomycin \pm gentamicin (or \pm rifampin)	For life-threatening infections
	Clindamycin (if strain susceptible)	For pneumonia, septic arthritis, osteomyelitis, skin or soft tissue infections
Alternative	*Vancomycin	
IV. Vancomycin-intermediately susceptible (MIC 4–8 μ g/mL) and vancomycin-resistant <i>S. aureus</i> (>16 μ g/mL)		
Drug of choice	Optimal therapy is unknown. Dependent on in vitro susceptibility test results. Various drugs which can be tried are: <ul style="list-style-type: none"> • Linezolid • Daptomycin • Quinupristin-dalfopristin • Telavancin 	
Alternative	<ul style="list-style-type: none"> • Vancomycin + linezolid \pm gentamicin • Vancomycin + trimethoprim-sulfamethoxazole 	

*Serum levels of vancomycin should be monitored, with peak concentrations.

PREVENTION

There are no approved antiStaphylococcal vaccines currently in the market. Handwashing with a detergent containing an iodophor, chlorhexidine or hexachlorophene is the most effective measure to prevent the spread of staphylococci. Constant surveillance for nosocomial Staphylococcal infections and careful attention to isolation procedures should be done in hospitals. Health-care workers identified as intranasal carriers of epidemic strain are treated with topical mupirocin and in some cases oral rifampin. Barrier precautions (gloves and gowns) minimize the contact with infected wounds, secretions and dressings. During an epidemic, all full-term infants in nursery are bathed with 3% hexachlorophene immediately after birth and the daily thereafter until discharge. Recurrent Staphylococcal furunculosis is treated with hexachlorophene washes, appropriate oral antimicrobial and nasal mupirocin. To prevent Staphylococcal food poisoning, individuals with Staphylococcal infections of the skin should not be allowed to prepare or handle the food. Once prepared, food should be eaten immediately or refrigerated appropriately to avoid the multiplication of organisms.

PROGNOSIS

Timely treatment with appropriate antibiotics reduces the morbidity and mortality. Without treatment, Staphylococcal septicemia has a mortality rate of more than 80%. A total leukocyte count less than 5,000/cumm or a polymorphonuclear leukocyte response of less than 50% is a grave prognostic sign. Prognosis is affected by various host factors like age, nutrition, immunocompetence and the presence of other debilitating diseases.

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IN A NUTSHELL

1. *Staphylococci* are aerobic or facultative anaerobic, catalase-positive, nonmotile, nonsporulating, gram-positive cocci that are ubiquitous in the environment.
2. Two species commonly associated with Staphylococcal disease in human are *S. aureus* and *S. epidermidis*.
3. *Staphylococci* are responsible for millions of community-acquired and health-care-associated infections.
4. Methicillin-resistant *S. aureus* has now become endemic in developing countries and can cause both hospital associated and community-acquired infections.
5. *Staphylococci* produce several virulence factors which can cause disease by either tissue invasion or through toxins.
6. *Staphylococci* can affect any system of the body and the infection ranges from trivial skin infection to lethal invasive disease.
7. The gold standard for diagnosis of Staphylococcal infection is isolation of the organism in cultures of infected specimen.
8. Treatment should be started with an antibiotic depending upon the severity of infection and the Staphylococcal susceptibility pattern of the area. Skin and soft tissue infection can be managed by oral antibiotics and drainage. For severe infections, parenteral therapy is indicated.
9. Constant surveillance for nosocomial Staphylococcal infections and careful attention to isolation procedures should be done in the hospitals. Handwashing is an effective measure to prevent the spread of infection.
10. Timely treatment with appropriate antibiotics reduces the morbidity and mortality. Vancomycin-resistant strains have been reported recently. This emphasizes the importance of rational use of antibiotics, isolation of the causative organism and its susceptibility testing.

Chapter 29.12

Neisseria Infections

Vidushi Mahajan

The two most important *Neisseria* infections are meningococcal disease, also known as epidemic cerebrospinal fever, caused by *Neisseria meningitidis* and gonorrhea caused by *Neisseria gonorrhoeae*. Incidence in India is not exactly clear owing to inadequate surveillance and sparse laboratory support for diagnosis. Meningococcal infections are more frequent in northern states of India. There have been numerous outbreaks of meningococcal disease in India, most recently in 2008–09 from North Eastern states, all attributable to serogroup A. As reported from sexually transmitted disease (STD) clinics, gonorrhea prevalence in Indian children varies between 5% and 10%.

NEISSERIA MENINGITIDIS

Etiology

Neisseria meningitidis has emerged as the third most common etiology of bacterial meningitis in Indian children below 5 years. It is a Gram-negative Diplococcus, seen as kidney-shaped pairs with adjacent sides flattened on Gram staining. *N. meningitidis* is fastidious. Growth occurs in a moist environment at 35–37°C in a 5–10% carbon dioxide atmosphere. Growth is readily supported by chocolate, blood, and Mueller-Hinton media.

Meningococci are commensal colonizers of the nasopharynx. Individuals who harbor these bacteria act as a reservoir of the bacteria. Humans are the only natural reservoir. The incubation period varies 3–4 days (range 1–10 days). Males are slightly more predisposed. Risk factors include young age (more than half cases occur in children less than 2 years), poor hygiene and overcrowded living conditions (e.g., military barracks). Indian Armed Forces is a high-risk group and suffers from 9–10 cases of meningococcal disease per year.

Pathogenesis

N. meningitidis is acquired mainly by the respiratory route. Invasion occurs following infection by new noncommensal strains or sometimes, facilitated by existing viral respiratory tract infection. Meningococci and gonococci produce an IgA protease that helps in colonization of mucous membranes by cleaving the proline-rich hinge region of secretory IgA. Meningococci invade nonciliated epithelial cells through their type IV pili. The pili attach to CD46 proteins on the epithelial cell surface which leads to cytoskeletal rearrangements in the host cell and endocytosis. Meningococci pass through the epithelium and enter the bloodstream. Serum antibody against meningococcal antigens, if present, can block this spread by complement-mediated bacterial lysis. Absence of antimeningococcal antibody is associated with development of meningococcemia. Two additional characteristics of meningococci contribute to its pathogenicity: its polysaccharide capsule and an iron scavenging system which uses host transferrin and lactoferrin.

Meningococcemia is associated with an acute inflammatory response including vasculitis and disseminated intravascular coagulation (DIC). There is activation of inflammatory cytokines (IL-1, IL-6, and TNF α) and of both the extrinsic and intrinsic pathways of coagulation. Blockage of small vessels by leukocyte-rich fibrin clots result in focal hemorrhage and necrosis in major organs particularly skin, heart, central nervous system, adrenals. Myocarditis occurs in more than 50% of patients. Diffuse adrenal hemorrhage without vasculitis known as *Waterhouse-Friderichsen syndrome* may also be seen.

Persons with primary complement, properdin, factor D, or terminal-component deficiency are at increased risk of developing meningococcemia. Recurrent infection is more common with terminal component deficiencies than with properdin deficiency. Also, increased risk is seen with the acquired complement deficiencies that occur in patients with nephrotic syndrome, vasculitis and chronic liver disease. Host factors like presence of factor V Leiden exacerbates *purpura fulminans* (prominent petechia/purpura with hypotension) but may not affect mortality.

Clinical Disease

Invasive meningococcal disease can have protean manifestations, like bacteremia alone, meningococcemia (sepsis), and meningitis with or without meningococcemia. Occult meningococcal bacteremia usually has nonspecific signs mimicking minor viral infections. This presentation may resolve spontaneously without antibiotics, or can lead to meningitis. Meningitis, the most common invasive meningococcal manifestation, presents with lethargy, headache, photophobia, vomiting, and signs of meningeal irritation.

Acute meningococcemia begins with nonspecific viral-like illness with fever, headache, myalgias, vomiting, and diarrhea. Often a maculopapular rash heralds the serious illness. The progression of serious disease may happen rapidly over hours to metabolic acidosis, renal failure, adrenal hemorrhage, DIC, septic shock, and coma. The dissemination may also involve joints (suppurative arthritis), pneumonia, and purulent pericarditis/myocarditis. In the recent epidemic reported from Shillong, (N = 110) following signs were recorded among children with invasive meningococcal disease: Fever (100%), headache (56%), vomiting (54%), altered sensorium (26%), purpura/petechiae (24%), seizures (9%) and excessive crying (5%). Meningeal signs were present in 78% and bulging anterior fontanel in 23% below the age of 18 months. Shock was seen in 38%.

For surveillance purpose the case definitions for probable and confirmed meningococcal disease in Indian setup have been proposed. *Probable case* includes suspected case of acute or bacterial meningitis and positivity for gram-negative Diplococci or ongoing epidemic or with Petechiae/purpura. *Confirmed cases* should have suspected or probable case of acute meningitis and cerebrospinal fluid (CSF)-positivity for *N. meningitidis* or culture-positivity for *N. meningitidis* in CSF or blood.

Outbreak Identification

Outbreak in India is defined as an attack rate greater than or equal to 5-fold higher than that seen in previous years in the same area, or if no data are available for that same area, an attack rate that is greater than or equal to 5-fold higher than that seen in similar areas OR probable and confirmed cases is greater than 5 cases/100,000 over a 3-month period OR incidence (probable or confirmed cases) increases for 3 consecutive weeks in the same area OR attack rate of greater than 3 cases of meningococcal disease in less than 3 months among persons residing in the same area who are not close contacts of each other, with a primary disease attack rate of greater than 10 primary cases/100,000.

Complications

Complications seen are due to meningococcemia and meningitis *per se* and immune complex-mediated which become apparent in the second week after the onset of illness. Suppurative complications include raised intracranial pressure (28%), coagulopathy (16%) and hepatopathy (10%) as seen in the recent epidemic from North-East. Herpes labialis was observed in 9% of cases. Mortality was high in those with metabolic complications of meningococcemia: syndrome of inappropriate antidiuretic hormone (SIADH), diabetes insipidus and cerebral salt wasting (13%). Meningococcal purpura fulminans were seen in 4.5% and less than 2% had subdural empyema and optic neuritis. Mortality was 6.4%.

Immune complex-mediated complications include arthritis and cutaneous vasculitis (erythema nodosum). The arthritis is mono or oligoarticular, involving large joints. Long-term sequelae are uncommon. Fever persisting beyond 7 days in a child with meningococcal illness should alert the physician to the possibility of immune complex-mediated complications.

Approach to Diagnosis

Diagnosis of meningococcal disease rests on isolation of the meningococci from blood, CSF, or synovial fluid. Nasopharyngeal isolation does not imply invasive disease. Prior antibiotic use, which is common in India, reduces the chances of positive culture. Meningococci sometimes can be identified in skin scrapings of petechial lesions. Bacteria may be seen on Gram staining of the buffy coat layer, of a centrifuged blood sample. Diagnosis is also supported by detection of meningococcal antigen in CSF by rapid latex agglutination tests, especially in the setting of partially treated infections or negative cultures. Antigen tests using serum or urine are not recommended. Polymerase chain reaction (PCR) in CSF/blood is now available at a few centers in India.

Other laboratory findings include anemia, neutropenia or leukocytosis with increased band forms, thrombocytopenia, hematuria and proteinuria. Patients with DIC have hypoalbuminemia, metabolic acidosis (high serum lactate) and deranged coagulation studies.

Differential Diagnosis

Meningococcal infection can have overlapping features with sepsis, meningitis, Rickettsial infections and bacterial endocarditis. Encephalitis and viral infections with echoviruses (particularly types 6, 9, and 16), coxsackieviruses (primarily types A2, A4, A9, and A16) may have to be ruled out. Autoimmune disorders like Henoch-Schönlein purpura, hemolytic-uremic syndrome, Kawasaki disease, idiopathic thrombocytopenic purpura, and drug rash can mimic meningococcal disease.

Management

Crystalline Penicillin is the drug of choice. Cefotaxime or ceftriaxone are acceptable alternatives in case of nonavailability or drug resistance. Chloramphenicol (75–100 mg/kg/24 hours divided q 6 hours IV) is used for children allergic to β -lactam antibiotics. Therapy is recommended for at least 7 days. Shock necessitates treatment with normal saline and inotropes. Children with fulminant meningococcemia with refractory shock may require hydrocortisone due to adrenal insufficiency. Extracorporeal membrane oxygenation has been used with limited success.

Outcome

Deafness occurs in 5–10% of children with meningococcal meningitis. Cerebral thrombosis leading to cerebral infarction can occur in severe cases. Rare neurologic sequelae like focal deficits, seizures, ataxia and obstructive hydrocephalus may be seen 3–4 weeks after onset of illness. Case fatality in severe disease forms like pyogenic meningitis or septicemia is 5–25% despite advancements in pediatric critical care.

Prevention

Vaccination (Also see Chapter 23.21 on Meningococcal Vaccines)

Routine immunization is not recommended currently. Vaccine is recommended only during outbreaks, in high risk children and international travelers. The two meningococcal conjugate vaccines (MCVs) licensed in India are: firstly a quadrivalent (A, C, W-135, Y) polysaccharide-protein conjugate vaccine MenACWY-D, Menactra[®]. Single dose of 0.5 mL IM is recommended in children above 2 years age. Two-doses of this vaccine is recommended in children aged

9–23 months. Studies suggest that effectiveness is 80% to 85% within 3 to 4 years after vaccination. Side effects include pain, swelling, and rare reports of Guillain-Barré Syndrome especially in adolescents. When MenACWY-D and PCV13 are administered concomitantly, interference in PCV13 immune responses was noted especially in patients with asplenia. Hence, it is recommended that at least one month interval should be kept between PCV13 and MenACWY-D, and PCV13 should be administered first. Second MCV is a monovalent serogroup A conjugate vaccine (PsA-TT, MenAfriVac[®]). The vaccine is immunogenic in adults but is unreliable in children younger than 2 years.

Mass Reactive Vaccination

In India it is carried when disease incidence is 10 cases/100,000 in a given district. Mass immunization with bivalent (A + C) polysaccharide vaccine was carried as a pilot project in India during the Meghalaya outbreaks.

Care of Contacts

Chemoprophylaxis is given to close contacts to eliminate nasopharyngeal carriage, preferably within 24 hours of contact with an index case. Ciprofloxacin is the drug of choice since only a single oral dosing is needed. Ceftriaxone is another alternative (125 mg stat IM for children < 12 years; 250 mg stat IM for > 12 years of age). Children may be given rifampin (10 mg/kg orally q 12 hours for a total of four doses; maximum dose: 600 mg; 5 mg/kg/dose for infants < 1 month of age)). Mass chemoprophylaxis is not considered to be useful or epidemiologically cost effective.

NEISSERIA GONORRHOEA

Gonorrhea is the most frequent sexually transmitted infection (STI) found in sexually abused children. It is an infection of the mucus membranes of the genitourinary tract and rarely, rectum, oropharynx and conjunctiva. Risk factors include unprotected sex, multiple sexual partners, homosexuality, poverty, presence of other STI. Gonococcal infection in the neonate results from perinatal exposure during birth. Universal screening for gonorrhea is not advised since gonococcal infections in females are commonly asymptomatic. For preadolescent girls, vaginitis is the most common symptom. Disseminated gonococcal infection may present as *tenosynovitis-dermatitis syndrome*, characterized by fever, rash, and polyarthralgia involving the wrists, hands, and fingers; or as *suppurative arthritis syndrome*, in which systemic signs are not marked and monoarticular arthritis, often involving the knee, occurs. Due to the legal implications involved, culture is the preferred method of diagnosis. Specimens from normally unsterile sites are streaked on a selective (e.g., Thayer-Martin or Martin-Lewis) medium and specimens from sterile sites are streaked on nonselective (e.g., chocolate agar) medium. Nucleic acid amplification testing (NAAT) is recommended under special circumstances. Serology is not recommended because it fails to denote an active infection. Cephalosporins are the sole class of antibiotics recommended for the treatment of *N. gonorrhoeae* infections. All children found to have gonorrhea should be tested for other STDs, including Chlamydia, syphilis, and HIV.

Treatment guidelines are summarized in **Box 1**.

BOX 1 Treatment of gonorrhea (CDC 2010)

1. For uncomplicated gonococcal infection: (Weight < 45 kg)
vulvovaginitis, cervicitis, urethritis, pharyngitis, proctitis
Ceftriaxone 125 mg IM in a single dose
2. For bacteremia/arthritis (Weight < = 45 kg)
Ceftriaxone 50 mg/kg IM or IV (max. 1 g) once a day for 7 days
3. For bacteremia/arthritis (Weight > 45 kg)
Ceftriaxone 50 mg/kg IM or IV (max. 1g) once a day for 7 days.

IN A NUTSHELL

1. Invasive meningococcal disease presents as meningitis, or meningococemia (sepsis) or both. It occurs in endemic as well as epidemic forms.
2. It is caused by gram-negative *Diplococcus*, *Neisseria meningitidis*, which are normal commensals of the nasopharynx in 5–10% of the population.
3. Young age (children < 2 years), overcrowded living conditions and complement deficiencies (both inherited and acquired) are important risk factors.
4. Children usually present with fever, headache, altered sensorium, purpura/petechiae, meningeal signs and seizures. More than one-third of the patients develop shock during course of illness. Complications due to inflammation include pneumonia, raised intracranial pressure, coagulopathy, hepatopathy, diffuse vasculitis, DIC, Waterhouse-Friderichsen syndrome, purpura fulminans and subdural empyema. Immune complex mediated complications include arthritis and erythema nodosum.
5. Diagnosis of meningococcal disease rests on isolation of meningococci from blood, CSF, or synovial fluid by culture, latex agglutination, or PCR and skin scrapings of petechial lesions.
6. Important differential diagnosis includes sepsis, Rickettsial infections, bacterial endocarditis, autoimmune vasculitides, coxsackie and echovirus infections.
7. Drug of choice is Penicillin G (250,000–400,000 U/kg/24 hours divided q 4–6 hours IV). Alternatively, cefotaxime or ceftriaxone maybe used. Isolation for at least 72 hours is advised.
8. Ciprofloxacin/ceftriaxone is used for chemoprophylaxis in close contacts. Meningococcal vaccination is recommended in select groups and in outbreak situations.

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Chapter 29.13

Pseudomonas Infections

Nupur Ganguly

Pseudomonas aeruginosa is an opportunistic pathogen of the Pseudomonadaceae family and causes infections usually in immunocompromised host. It is one of the most important causes of nosocomial infection. Its ubiquitous presence and minimal nutritional needs causes easy colonization and develop reservoirs in sinks or respiratory equipment in hospital setting. Prolonged hospital stay, mechanical ventilation, and central line catheters cause breach in host defense and predisposes to *Pseudomonas* infection. *Pseudomonas aeruginosa* has a wide potential to develop resistance to multiple antibiotics by various mechanisms and inappropriate empirical therapy increases the possibility of development of such resistance. Multidrug resistance (MDR) *Pseudomonas*, resistant to at least 3 out of 4 classes of antibiotic, i.e., antipseudomonal penicillin (piperacillin, cephalosporins), Carbapenems, fluoroquinolones and aminoglycoside, is an emerging challenge for associated mortality, morbidity and high cost of therapy.

EPIDEMIOLOGY

Pseudomonas aeruginosa is a gram-negative nonfermenting aerobic bacillus (can grow anaerobically if nitrate is available). It is mostly present in moist environment, and easily colonise in sinks, respiratory equipment, mops and disinfectants; even it can survive in distilled water. Being an opportunistic pathogen impaired host defense is the prerequisite to develop infection. These infections further spread from patient to patient on the hands of hospital personnel, by direct patient contact or with the contaminated reservoirs. In developing countries *Pseudomonas* is a common pathogen in burn wound, febrile neutropenia and patients undergoing chemotherapy and causes most serious infection in ventilator associated pneumonia. It is also the leading cause of chronic lung infection and respiratory failure in cystic fibrosis.

PATHOGENESIS

Pseudomonas aeruginosa has various invasive and virulence factor causing acute and chronic infection. The surface virulence factor (flagella, pili and lipopolysaccharide) helps in attachment, colonization and invasion. Secreted virulence factor (mucoid, exopolysaccharides, exotoxin A and proteases) damages tissue and produces cytokines causing tissue damage. Impaired host defense mechanism further contributes to the virulence and chronicity of infection.

Its single polar flagellum helps in motility and adhesiveness to the cell surface for initiation of infection. The pili present in the outer surface membrane of *Pseudomonas*, attaches to the epithelial cells at the site of colonization and forms a nidus for local infection. In immunocompromised host it becomes locally invasive and cause systemic infection. Several toxins produced by *Pseudomonas* counteract the host defense mechanism. Among them exotoxin A causes tissue necrosis, Type III secretion system (TTSS) injects four types of exotoxin (ExoU, ExoS, ExoT, and ExoY). ExoU, are more toxic, and are associated with poor outcome and increased mortality in ventilator associated pneumonia (VAP). Pyocyanin is responsible for greenish sputum in *Pseudomonas* infection, causes epithelial and endothelial damage to the lung tissue in acute infection. Like majority of other organisms, *P. aeruginosa* needs iron to sustain growth. Pyochelin a derivative of pyocyanin is a siderophore helps in deriving iron from the host cell for bacterial growth. *Pseudomonas aeruginosa* in presence of large bacterial mass communicates with each other through

the system of quorum sensing (QS), in response they secrete inflammatory mediators increasing the virulence of the organism. Quorum sensing system also helps in the formation of biofilm.

CLINICAL FEATURES

Pseudomonas aeruginosa rarely infects the healthy tissues, however, in presence of impaired host response, it can infect any tissue. Among them the most common infections are as follows:

Bloodstream Infection

Disseminated bacterial infection is seen in burns, neutropenia and malignancies where patient is undergoing chemotherapy. It has a grave prognosis and the mortality is about 50%. The clinical presentation of septicemia is same as with other gram-negative infection and patient may present in shock. A typical vasculitic skin lesion which differentiates from other gram-negative infection is ecthyma gangrenosum. They are small painful hemorrhagic lesion with necrosis, pink in color to start with and become gangrenous.

Ventilator Associated Pneumonia

In ventilated patient initial slow colonization of *Pseudomonas aeruginosa* may lead to rapid fulminant infection. Patient presents with fever, chill, cough, cyanosis and tachypnea, X-ray shows bilateral opacities often with cavity formation. Isolation of the bacteria from sputum and bronchoalveolar lavage is diagnostic.

Urinary Tract Infection

Prolonged use of catheter, instrumentation and urinary tract obstruction predisposes to *Pseudomonas* infection. They have a complicated course and needs prolonged treatment.

Pseudomonas Dermatitis

Though less severe, community infections occur as folliculitis following bath in swimming pools, paronychia, and toe web infection seen with prolonged exposure to water. Puncture wound infection through shoes can give rise to serious infection. The bluish or greenish color pus is suggestive of *Pseudomonas* infection and is due to the pigment pyocyanin.

Eye and Ear

Pseudomonas is a predominant cause of otitis externa and severe ophthalmic infection (corneal keratitis) following prolonged use of contact lens.

Cystic Fibrosis

Chronic infection is commonly seen in patients with cystic fibrosis. In cystic fibrosis mucoid strains of *Pseudomonas* produce large amount of exopolysaccharide (alginate) to form biofilm. The biofilm helps in anchoring the bacteria to respiratory tract, impairs the ciliary movement facilitating colonization. Initial colonizations with nonmucoid strains are slowly replaced with the mucoid strain. These mucoid strains resist phagocytosis and host immune response by the biofilm formation leading to chronicity of the disease with frequent exacerbation. Due to repeated use of antibiotics the organism develops resistance to multiple antibiotics.

DIAGNOSIS

Clinical suspicion and certain clues like features of sepsis developed in immunocompromised host in ICU setting, greenish or bluish pus in abscess or greenish sputum in cystic fibrosis are suggestive of *Pseudomonas* infection. Due to easy colonization, simple isolation of the organism from the biological tissue is not diagnostic. Isolation of the bacteria from the central body fluid, external devices is diagnostic in the high risk individual.

MECHANISM OF RESISTANCE

P. aeruginosa causes resistance by various mechanisms leading to MDR infection. Different mechanisms of resistance are discussed below:

Altered Porins

It does not have the usual trimeric porins characteristic of enteric bacteria, instead it has monomeric porin, which reduces the membrane permeability of the drug leading to very slow entry. The mechanism operates for chloramphenicol and aminoglycosides.

Active Efflux

Active efflux system (MexAB-OprM) causes expulsion of the antibiotic out of the cell and thus increasing the Minimum inhibitory concentration (MIC) of the drug. In *Pseudomonas* infection efflux mechanism is the major factor contributing resistance to aminoglycosides, fluoroquinolones, and many beta-lactams. It is either chromosomal or plasmid mediated.

Bacterial Destruction

Bacterial destruction of beta-lactams by beta-lactamases enzyme is another common method of resistance in *Pseudomonas* infection. They are plasmid encoded mutated enzymes. Carbapenemases have wider spectrum of activity and not only hydrolyses carbapenems (meropenem, doripenem and imipenem) but also other beta lactams, e.g., cefotaxime and ceftazidime. They cannot hydrolyze monobactam (aztreonam) and are not inhibited by clavulanate.

Mutation

Fluoroquinolone resistance is caused by mutation of DNA gyrase.

Often all these mechanisms are present simultaneously causing MDR phenotypes. In cystic fibrosis formation of biofilm is also a major contributing factor for drug resistant infection.

TREATMENT

Due to the high mortality of *Pseudomonas* infection empirical therapy is often initiated. The choice of antibiotic in empirical therapy should depend on the age, site of infection, local resistance and prior use of certain antibiotics, including broad-spectrum cephalosporins, aminoglycosides, carbapenems, fluoroquinolones and hospital culture data. Combination therapy for empiric treatment is indicated in certain high risk patients, in severe infection and it should be prompt, as delay in therapy may lead to increased mortality. All infected catheters and devices should be removed, and abscesses should be drained whenever possible. The following antibiotics usually have reasonably good activity against *P. aeruginosa* and can be used alone as single agents if isolates are susceptible by in vitro testing: (a) beta-lactam and beta-lactamase inhibitor: ticarcillin-clavulanate, piperacillin-tazobactam; (b) Cephalosporins: ceftazidime, cefoperazone, cefepime; (c) Monobactam: aztreonam; (d) Fluoroquinolones: ciprofloxacin, levofloxacin; and (e) Carbapenems: meropenem, doripenem, imipenem. Doripenem has the least resistance amongst the three.

Alternative Antibiotics

When choice is limited in MDR *P. aeruginosa* infection, intravenous colistin and polymyxin B are alternative drugs. Colistin has a tendency for ototoxicity and nephrotoxicity, and requires dose adjustment in impaired renal function.

Adjunctive Antibiotics

Aminoglycosides (gentamicin, tobramycin and amikacin) should not be used as monotherapy due to their poor efficacy. They are effective when used in combination with the first line drugs in serious infection.

Inhaled Antibiotics

Inhaled tobramycin, gentamicin, polymyxins and colistin may be used in cystic fibrosis as an adjunct therapy for pneumonia and to prevent bronchiectasis.

Efflux Pump Inhibitors (EPI)

They are the newer modalities of treatment in the pipeline. These antibiotics target the active efflux mechanism of drug resistance.

COMBINATION VERSUS MONOTHERAPY

For combination therapy a beta-lactam is combined with aminoglycoside in the absence of any contraindication for the use of aminoglycoside, otherwise fluoroquinolone can be an alternative choice. Indications of combination therapy are severe sepsis or septic shock; neutropenic patients with bacteremia; burn patients; and endocarditis. However, controversy exists regarding the superiority of combination to monotherapy. In a meta-analysis of randomized control trial including immunocompromised patients with documented sepsis, combination therapy has not shown any reduction in mortality.

IN A NUTSHELL

1. *Pseudomonas aeruginosa* is an opportunistic pathogen of the Pseudomonadaceae family and causes infections usually in immunocompromised host.
2. It is one of the most important causes of nosocomial infections including, bacteremia, ventilator associated pneumonia, catheter infections.
3. *Pseudomonas* is an important infection in children with cystic fibrosis.
4. Piperacillin-tazobactam; ceftazidime, cefoperazone, cefepime; aztreonam; ciprofloxacin, levofloxacin; and meropenem, doripenem, imipenem have good activity against *Pseudomonas*.
5. Multidrug resistance (MDR) *Pseudomonas*, resistant to at least 3 out of 4 classes of antibiotic, i.e., antipseudomonal penicillin (piperacillin, cephalosporins), carbapenems, fluoroquinolones and aminoglycoside, is an emerging challenge.

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Chapter 29.14

Leptospirosis

Janani Sankar

Leptospirosis is an infectious disease caused by pathogenic organisms belonging to the genus *Leptospira*, and transmitted directly or indirectly from animals to humans. Human-to-human transmission occurs rarely. The disease can range from a subclinical infection to a serious multi organ involvement.

ETIOLOGY

Leptospira are aerobic bacteria. *Leptospira interrogans* is the pathogenic species that causes the disease and it has more than 250 serovars and each serovar can cause different syndromes. For example, the serovar *Leptospira icterohaemorrhagiae* usually causes hepatitis.

EPIDEMIOLOGY

Cattle, buffaloes, horses, sheep, goat, pigs, dogs and rodents are common reservoirs of leptospires. Rodents were the first recognized carriers of leptospirosis. They are the only major animal species that can shed leptospires throughout their lifespan without clinical manifestations, i.e., prolonged carrier state. They are incriminated as a primary source of infection to human beings. Although serovars icterohaemorrhagiae, Copenhageni, Grippotyphosa and Ballum have been often associated with rodents, other serovars like Pomona, Canicola and Hebdomadis have also been isolated.

PATHOGENESIS

Leptospires enter humans through abrasions and cuts in the skin or through mucous membranes. After penetration to the blood stream they cause endothelial lining damage of blood vessels and also cause ischemic damage of end organs.

CLINICAL FEATURES

Anicteric Form

The clinical presentation of leptospirosis varies widely. It can range from an acute febrile illness to a severe syndrome of multiorgan dysfunction. The more common, mild, anicteric form of the disease is characterized by nonspecific symptoms such as fever, headache, chills and severe myalgia restricting mobility. It may closely mimic acute infectious polyradiculomyelitis. CPK enzyme levels are usually very high. It may present with lymphadenopathy and generalized maculopapular rash mimicking mucocutaneous lymph node syndrome. Other manifestations include meningoencephalitis where children have severe headache and neck stiffness. CSF shows mildly elevated protein and lymphocytosis. Neuroimaging may show leptomeningeal enhancement. CSF dark field microscopy for leptospires may be positive.

Similar to enteroviral infections, it can cause myocarditis which is more common in infants and toddlers. A short febrile illness with disproportionate tachycardia, muffled heart sounds and cardiomegaly with or without raised CPK MB is usually the clinical picture. Apart from parenteral crystalline penicillin these children need inotropes and hemodynamic monitoring. Polyserositis is usually seen in the form of pleural effusion, pericardial fluid, ascites and gallbladder wall edema. This is usually associated with reduced serum albumin and occasionally these fluids may test positive for dark field microscopy. Transient glomerular dysfunction which closely mimics nephrotic syndrome is seen in

some children. Hepatorenal syndrome is a more serious condition which may require peritoneal or hemodialysis. It can involve the eyes and cause severe conjunctival congestion and uveitis.

Weil Syndrome (Icteric Form)

The illness closely mimics acute viral hepatitis and the probable differentiating features may be the presence of polyserositis and cholecystitis. This is a severe form of the infection, occurs less commonly in children and can sometimes coexist with hepatitis A infection. When it coexists with hepatitis A infection the severity and the duration of illness is longer. Renal manifestations are common, with abnormal urine analysis (hematuria, proteinuria, and hyaline and granular casts) and azotemia, which is often associated with oliguria/anuria. Acute renal failure occurs in a few cases and is the most common cause of mortality. Both acute renal failure and jaundice are less common in children than in adults.

APPROACH TO DIAGNOSIS

A high index of suspicion is usually required to diagnose Leptospirosis. It is usually suspected in the clinical context of fever with myalgia with history of contact with animals. A *confirmed case* of leptospirosis is one where the clinical specimens are culture positive for leptospira or the clinical symptoms are compatible with the disease and there is seroconversion or a fourfold rise in microscopic agglutination titer between acute and convalescent sera (taken at least 2 weeks apart and studied in same laboratory). A *presumptive case* is one where the clinical symptoms are compatible with the disease and microscopic agglutination titer is 1:100 or greater, there is a positive macroscopic agglutination slide test reaction on a single serum specimen obtained after onset of the symptoms, or there is a stable microscopic agglutination titer of 1:100 or more in two or more serum specimens obtained after onset of symptoms.

Modified Faine's criteria (Table 1) used for diagnosis of leptospirosis in adults, has also been found to be useful in older children. The Indian Leptospirosis Society has also laid down certain criteria for clinically suspecting leptospirosis. According to these criteria, leptospirosis should be suspected in a child presenting with a history of abrupt onset of high fever (> 39°C) and bodyache/headache, with any one or more of the following features: (i) jaundice, (ii) oliguria, (iii) cough and breathlessness, (iv) hemorrhagic tendency, and (v) signs of meningeal irritation or altered sensorium or convulsions.

Laboratory Investigations

The total count is usually higher with polymorphonuclear predominance and toxic granulation in the neutrophils. The platelet count is usually reduced.

C-reactive protein (CRP) may be positive and serum albumin levels may be low, more so in children with polyserositis. Bilirubin and liver transaminases are raised in icteric leptospirosis. Creatinine phosphokinase (CPK) may be raised in children presenting with myalgia and Creatinine Phosphokinase Muscle-Brain Fraction (CPK-MB) may be raised in children with myocardial involvement.

Serological Tests

Serological tests are usually preferred for confirmation of diagnosis. Detection of IgM antibodies during the second week of illness is the most sensitive test. A single high or a fourfold rise in IgG titer in paired samples is also suggestive of the infection. Slide agglutination method, Dri-Dot assay, LEPTO Dipstick, latex agglutination, complement fixation assay, indirect immunofluorescent test, and indirect hemagglutination test are the other tests with high sensitivity. DNA hybridization techniques or nucleic acid amplification procedures, including polymerase chain reaction

Table 1 Modified Faine's criteria for diagnosis of leptospirosis

Part A: Clinical data	
Question	Score
Headache	2
Fever	2
Temperature > 39°C	2
Conjunctival suffusion	4
Meningism	4
Muscle pain	4
Conjunctival suffusion	
+ Meningism	10
+ Muscle pain	
Jaundice	1
Albuminuria/Nitrogen retention	2
Total score	
Part B: Epidemiological factors	
Question	Score
Rainfall	5
Contact with contaminated environment	4
Animal contact	1
Total score	
Part C: Bacteriological and laboratory findings	
Isolation of leptospira in culture—Diagnosis certain	
Positive serology	Score
ELISA IgM positive*	15
SAT—positive	15
Mat—single high titer*	15
Rising titre (paired sera)	25
Total score	

*Any one of the tests only should be scored. By modified Faine's criteria score of ≥ 26 when using Part A, Part A+B or ≥ 25 using Part A+B can be considered as current leptospirosis.

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(PCR) and Warthin-Starry Silver staining polymerase chain reaction and immunohistochemical methods can be used to detect the presence of leptospira in body fluids or culture supernatants. The microscopic agglutination test (MAT) (serogroup-specific assay) using live antigen suspension of leptospiral serovars is the gold standard. This test is not helpful for diagnosing leptospirosis during the acute illness; however, it remains important for epidemiological research purposes. The test is read by dark-field microscopy for agglutination and the titers are determined; a four-fold or greater increase in titer in paired sera is confirmative. Agglutinins usually appear by the second week of illness and reach the maximum titer by the 4th week. Due to lack of specific live serovars MAT is not regularly done. MAT titer of 1:100 is usually seen in the general population in endemic area and does not suggest active infection. High titers are usually required to make a diagnosis of active disease.

Demonstration of Organism in Cultures

Though not easily available and not used in practice, demonstration of the organisms in the patient's blood and culture of the organism can be used for diagnosis before the second week of the illness. *Leptospira* can be recovered from the blood or CSF during the first 10 days of illness and from the urine after 14 days.

TREATMENT

Leptospirosis usually responds to oral amoxicillin (50–100 mg/kg/day for 7 days), azithromycin (10 mg/kg/day for 3 days), cefixime (10 mg/kg/day for 7 days) or doxycycline (5–10 mg/kg/day for 7 days). Antibiotic administration especially before the 7th day of illness reduces length of hospitalization and leptospiruria. In children, even late institution of antibiotic treatment has been shown to prevent complications. Treatment with parenteral penicillin 50,000–100,000 U/kg/day is usually reserved for very sick children with meningoencephalitis, myocarditis and renal involvement.

Adequate attention to supportive care, including maintenance of the fluid-electrolyte balance, treatment of cardiovascular collapse, and provision of dialysis for renal failure, are equally important. Frequent monitoring of vital parameters and hemodynamic assessment, careful charting of fluid input and output, and prompt use of ionotropes in patients with hypotension refractory to fluid therapy are important considerations in the management of the disease.

PREVENTION

Prevention is usually achieved by controlling the reservoir or reducing infection in animal reservoir populations such as dogs or livestock. Prevention and control should be targeted at the infection source; and the route of transmission between the infection source and the human host.

It is important to target reduction of animal reservoir populations like rats and immunization of live stocks.

PROGNOSIS

It usually depends upon the type of clinical illness. The milder forms and the anicteric usually respond to oral drugs and recover completely. The severe type with multi organ involvement like acute respiratory distress syndrome (ARDS), myocarditis, liver cell failure and renal failure is usually associated with high mortality.

IN A NUTSHELL

1. Leptospirosis is a zoonosis caused by pathogenic organisms belonging to the genus *Leptospira*, and transmitted directly or indirectly from animals to humans.
2. Rodents are incriminated as a primary source of infection to human beings.
3. The clinical presentation of leptospirosis varies widely. It can range from an acute febrile illness to a severe syndrome of multiorgan dysfunction. Two main forms are anicteric form and icteric presentation (Weil disease).
4. Weil syndrome closely mimics acute viral hepatitis. Polyserositis and cholecystitis are additional features.
5. The microscopic agglutination test (MAT) (serogroup-specific assay) using live antigen suspension of leptospiral serovars is the gold standard for diagnosis.
6. Leptospirosis usually responds to oral amoxicillin, azithromycin, cefixime, or doxycycline.

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Chapter 29.15

Plague

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Plague is an infectious disease of rodents which is transmitted to man through the bite of infected ectoparasite (rat-flea) caused by the bacteria *Yersinia pestis*. It is primarily a zoonosis involving rats and rat-fleas with man being an intermediate host. The first mention of plague dates back to 1320 BC. In AD 542, a record 100 million people died of it in Europe. Due to associated high mortality, plague has also been referred to as *black death*. The first reported outbreak of plague in India occurred in the early part of the seventeenth century. Plague often occurs in epidemics and is characterized by rapidly developing infection with severe toxemia and a grave prognosis in the absence of treatment.

There are certain well known world foci from which epidemics have been known to originate, after periods of inactivity. Although the most modern pandemic, occurring at the end of the last century, has continued to decline, outbreaks have emphasized the continued presence of virulent bacteria in India, Cambodia, Vietnam, Indonesia, Africa, Brazil, Argentina, Chile, and Peru. In 2004, India reported a localized outbreak of bubonic plague in the Dangud village, district of Uttarkashi.

ETIOLOGY

The genus *Yersinia* is in the family, enterobacteriaceae and is composed of 11 species. Among them, *Yersinia enterocolitica*, *Yersinia pseudotuberculosis* and *Yersinia pestis* are pathogenic for humans and animals. These organisms usually infect rodents, pigs and birds. Humans are the accidental hosts. *Yersinia pestis* is transmitted by fleas or in aerosols and it is the cause of plague. *Yersinia enterocolitica* and *Yersinia pseudotuberculosis* cause enterocolitis.

Yersinia pestis is a gram-negative nonmotile, nonspore forming, intracellular coccobacillus. The bacteria can be isolated from blood, sputum or enlarged lymph nodes during the active disease. Virulence is determined by antigens V, W, envelope of fraction I, purine synthesis, and production of both exotoxin and endotoxin. The organism has several chromosomal and plasmid related factors. These factors are responsible for its virulence and survival in mammalian hosts and fleas. Its bipolar staining appearance is shared with *Yersinia pseudotuberculosis*. The biochemical reactions, serological tests, phage sensitivity and molecular techniques can differentiate *Yersinia pestis* from *Yersinia pseudotuberculosis*.

EPIDEMIOLOGY

Plague is basically maintained in nature by rats and other rodents. These rodents include mice, skunks, squirrels, gophers, and rabbits. Dogs and cats have also been implicated in human cases. Principal hosts in India are the wild and domestic rats—*Tatera indica* and *Rattus rattus*. Infection persists as a chronic disease of wild rodents and maintained by the insect vector.

Vector

Plague is transmitted by the bite of insect vectors, the most common being the rat-flea, i.e., *Xenopsylla cheopis*. Other uncommon vectors include *X. brasiliensis* and *Diamanus montanus*. The infected flea regurgitates a large number of bacteria into the bloodstream of the host during feeding. When another rat-flea bites the host, it ingests the infected blood. A clot is formed in the proventriculus of the

flea by the action of enzymes produced by both *Y. pestis* (coagulase) and the flea (trypsin). The clot blocks the flea's alimentary tract, propagating bacterial multiplication. When this flea bites another host, it discharges huge numbers of *Y. pestis* into its bloodstream. Formation of clot occurs at low ambient temperatures explaining the abatement of plague epidemic in summer months.

Host and Environment

Plague can occur at all ages and in both sexes. Man does not possess any natural immunity to *Y. pestis*. Asymptomatic carrier state, though rare, is known to occur. Plague epidemics occur more commonly in winter months. During monsoon, heavy rainfall will flood the rat burrows and stop the transmission. Natural or man-made calamities like earthquakes and wars have been found to be associated with outbreaks of plague in the past.

PATHOGENESIS

Humans can acquire plague by (i) bite of an infected flea; or (ii) inhalation of infected droplets from a case of pneumonic plague. In rare cases, the organism may enter through pharynx or conjunctiva. Rat-flea attacks the man only if rats are not available immediately. This situation arises in an epizootic, characterized by death of large number of infected rodents.

The spread among human population occurs by the respiratory route. Airborne droplet nuclei are discharged by the cases suffering from pneumonic plague. Bubonic plague cannot spread from person to person because the bacilli are locked inside the bubo and are not accessible to outside world until the bubo ruptures. Role of asymptomatic carrier in transmission of disease is not clear.

The infected fleas inoculate the organisms into skin of the patient while feeding. These organisms are drained to regional lymph nodes where they replicate and it results in bubonic plague, the most common form of plague. If the patient does not get specific therapy promptly, it may cause bacteremia, resulting in purulent, necrotic and hemorrhagic lesions in several organs. The pneumonic plague is due to inhalation of infected material. The pneumonic plague is highly transmissible type of plague. The domestic cats with pneumonic infection are also responsible for transmission of the disease. Due to high transmissibility and high morbidity as well as mortality, *Yersinia pestis* is considered as an important threat for its use as a biological weapon.

CLINICAL MANIFESTATIONS

Yersinia pestis infection has very wide spectrum of clinical presentation, starting from asymptomatic to severe fatal clinical syndrome. Bubonic plague, Pneumonic plague, Septicemia and Meningitis are main clinical presentations of the disease.

Bubonic Plague

Bubonic plague accounts for 80–90% of cases. There is an incubation period of 2–8 days after a fleabite. From 2–8 days after a fleabite, tender, nonfluctuating lymphadenitis (bubo) develops in regional lymphatics draining the bite area. The development of bubo depends upon the site of inoculation. The inguinal region is the most common site for development of bubo. Axillary and cervical regions are other known areas for its development. A papule, vesicle or ulcer at the inoculation site develops in approximately 25% of cases. Tenderness of the involved nodes is remarkable. It may cause suppuration in about 20% cases. The patient tries to avoid movement or pressure on the bubo. In 90% of cases, the bubo is unilateral and can be up to 10 cm in diameter. Although the onset of fever usually coincides with development of adenitis,

fever can occur days before it. There is a rapid rise in temperature (about 39.4°C) with chills, headache, malaise, anorexia, vomiting, myalgia and prostration during the hematogenous spread from the infected bubo. The skin may show insect bites and scratch marks. Localized cellulitis or abscess at the flea bite site is rare. Endotoxic shock is followed in a few days by death in the absence of specific antibiotics therapy. Purpura and gangrene of extremities may develop in relation to intravascular coagulopathy. Untreated plague has a mortality of about 50%. The death may occur within 2 to 4 days after onset of symptoms.

Pneumonic Plague

Pneumonia (16% of cases) can occur by inhalation (primary plague pneumonia) or by hematogenous seeding of bubonic or septicemic plague (secondary pneumonia). Pneumonic plague is the least common but most dangerous and fatal form of the disease. It may cause chest pain, progressive tachypnea, dyspnea, hypoxia and productive cough. The sputum may be frothy, blood-tinged, hemorrhagic or purulent. Chest X-ray typically shows alveolar infiltrations. In cases related to inhalation of secretions from infected animals or humans, extensive bronchopneumonia with cavities may develop. Primary plague pneumonia can progress quickly and may result in death even on the first day of symptoms. Plague pneumonia develops more commonly in patients with septicemia than in those with bubonic plague.

Other Manifestations

Septicemic plague occurs in 15–25% of cases. It is characterized by severe endotoxemia and multiorgan failure. Untreated, 100% cases are fatal. Even with treatment, the mortality is more than 30% in this group. The abdominal pain, nausea, vomiting and diarrhea like symptoms may be confusing and misleading. Plague can manifest as septicemia without a bubo. Tonsillitis and gastroenteritis are also known to occur in plague. These manifestations may or may not be associated with bubo formation and lymphadenopathy.

Meningitis

Altered sensorium with lethargy, stupor or delirium is common, but meningitis may be a complication of bubonic plague, particularly occurring in individuals who have been inadequately treated. Meningitis is more common in children than in adults. It occurs in 10% of children with plague.

LABORATORY FINDINGS

Leukocytosis in the range of 10,000–20,000/cu mm is common with shift to the left. Staining of clinical specimens (lymph node aspirates, blood, sputum, exudates) with Gram, Wayson or Giemsa stains may reveal characteristics bipolar staining coccobacilli. In patients with pulmonary involvement sputum is purulent and loaded with bipolar staining gram-negative, pleomorphic coccobacilli. Diagnosis can also be made by polychromatic or fluorescent antibody methods, antigen detection, or PCR. Needle aspirate specimens from infected nodes yield growth of organisms in about 75% of patients. *Yersinia pestis* grows in routine culture media, including blood agar, within 48 hours. Culture of blood specimens has positive results in about 60% of children with bubonic plague and in about 100% of those with septicemic plague. Quantitative blood culture data suggest that a bacterial density greater than 10^2 organisms/mL is associated with a greater risk of hypotension and shock. Cerebrospinal fluid in meningitic plague has features typical of bacterial meningitis such as polymorphonuclear leukocytosis and positive Gram stain.

Serological testing is useful retrospectively. Convalescent serum specimens are collected 4 weeks after onset of illness. Passive hemagglutination test, enzyme immunosorbant assay (EIA) and dot EIA have been used to detect immunoglobulin G antibodies against *Yersinia pestis*.

TREATMENT

Patients suspected of having bubonic plague should be placed in isolation until 2 days after starting antibiotic treatment to prevent the potential spread of the disease. Bubonic plague is treated with injection streptomycin 30 mg/kg/day, divided in two doses by intramuscular route for 10 days. Streptomycin is inappropriate for septicemic plague because of its erratic absorption. Gentamicin (2.5 mg/kg IM/IV three times daily), doxycycline (< 45 kg: 4.4 mg/kg/day, divided in 2 doses, IV; > 45 kg: 100 mg every 12 hours IV or 200 mg IV once daily) or chloramphenicol (25 mg/kg (maximum 500 mg) orally or IV four times daily for 10 days) should be preferred for septicemia and meningitis. Another alternate is ciprofloxacin 30 mg/kg/day IV twice daily (20 mg/kg orally twice daily) for 10 days. Resistance and relapses to gentamicin, doxycycline, chloramphenicol and ciprofloxacin are rare. *Yersinia pestis* may be susceptible to penicillin in vivo, but it is ineffective in treatment of human disease and therefore penicillin should not be used. Clinical improvement is noted within 48 h of initiating treatment.

Postexposure Prophylaxis

The close contacts of patients with pneumonic plague should be given post exposure prophylaxis. Contacts of cases of uncomplicated bubonic plague do not require prophylaxis. Antimicrobial prophylaxis is recommended within 7 days of exposure for persons with direct, close contact with a pneumonic plague patient or those exposed to an accidental or terrorist induced aerosol. Tetracycline or doxycycline or TMP-SMZ should be given for 7 days as postexposure prophylaxis.

PREVENTION AND CONTROL

Clinical suspicion during an outbreak should be given paramount importance. The diagnosis of plague should be considered if cases of the following clinical presentations occur in previously healthy patients, especially if two or more cases arise that are linked in time and place:

- Sudden onset of severe, unexplained febrile respiratory illness;
- Unexplained death following a short febrile illness;
- Sepsis with gram-negative coccobacilli identified from clinical specimens.

The level of suspicion of plague depends on local circumstances at the time—in the event of a known or suspected deliberate release, or among contacts of plague cases, the threshold for making a diagnosis of plague should be lower. If plague is suspected, microbiological specimens should be sent for assay, and consideration should be given to initiating empirical treatment pending results.

The bacilli can be demonstrated in a stained smear from bubonic fluid or sputum. Pus, sputum, and blood can be cultured to grow the organism. Antibodies can be detected in serum of convalescent patients 7–10 days after the onset of disease.

Control of Rats

Rats can be killed by trapping or poisoning them. Rats should be denied three basic requirements essential for their survival, i.e., food, water, and shelter. Food supply of the rats can be reduced

by improving general sanitation, proper disposal of trash and wastes, and properly storing the food meant for human use. Rat burrows can be eliminated by filling them up with a solid material. The burrows can also be fumigated by using calcium cyanide (cyanogas) or carbon-disulfide. Suppression of rodent population during an epidemic should always be associated with anti-flea measures.

Control of Rat-fleas

The insect vector should be eliminated by using an appropriate insecticide. Dichlorodiphenyltrichloroethane (DDT) used to be the insecticide of choice, but of late, several species of flea have become resistant to it. Other commonly used insecticides for flea control include beta-Hexachlorocyclohexane (BHC) and aldrin. The insecticide spray should be carried out both in houses and fields.

Active Immunization

Routine vaccination is not recommended for prevention of plague. The inactivated vaccine, consisting of formalin-killed bacteria, is no longer available. This vaccine had uncertain efficacy in protecting humans, particularly from plague pneumonia, and the long time interval to produce antibodies means that it would be ineffective in the event of a deliberate release of the organism. New sub-unit vaccines are being developed and have much greater efficacy in mice even against plague pneumonia, but have not yet been evaluated for immunogenicity in humans.

Vaccines are not recommended for immediate protection in outbreak situations. Vaccination is only recommended as a prophylactic measure for high-risk groups (e.g., laboratory personnel who are constantly exposed to the risk of contamination). A live attenuated vaccine administered by aerosol is under trial for usage in pneumonic plague.

Health Education

The local community should be educated and trained to eliminate rodents and their breeding places. They should be cautioned against handling dead rats. Maintenance of sanitation and hygiene should be emphasized upon. Factors affecting the transmission and possible preventive strategies should be highlighted.

Surveillance

Plague is a notifiable disease. Periodic surveys should be performed to estimate the extent of infected rats and fleas. Effective control measures should be established well in advance of an outbreak.

IN A NUTSHELL

1. Plague is an infectious disease of rodents which is transmitted to man through the bite of infected ectoparasite (rat-flea) caused by the bacteria *Yersinia pestis*.
2. Plague is transmitted by the bite of insect vectors, the most common being the rat-flea, i.e., *Xenopsylla cheopis*.
3. Humans can acquire plague by (i) bite of an infected flea; or (ii) inhalation of infected droplets from a case of pneumonic plague.
4. *Yersinia pestis* infection has very wide spectrum of clinical presentation, starting from asymptomatic to severe fatal clinical syndrome. Bubonic plague, pneumonic plague, septicemia and meningitis are main clinical presentations of the disease.
5. Streptomycin is the antibiotic of choice for bubonic plague. *S. pneumonic* and septicemic plague may be treated with gentamicin, doxycycline, chloramphenicol or ciprofloxacin.

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Chapter 29.16

Brucellosis

Sriram Krishnamurthy

Brucellosis is the most common zoonosis worldwide, and is caused by organisms of the genus *Brucella*. Humans become infected by ingesting animal food products, direct contact with infected animals, or inhaling infectious aerosols (from animal dung or contaminated dust) either by accident or as a result of bioterrorism.

Brucellosis was known to be an occupational disease in animal husbandry and abattoir workers, but is now considered to be primarily a disease associated with the ingestion of unpasteurized milk or dairy products. Clinically, brucellosis is an enigmatic disease. A more often encountered insidious onset of the disease, undulating nature of symptoms, and protean manifestations involving almost any organ system of the body often make the diagnosis difficult. Morbidity in untreated brucellosis is significant. Hence, early diagnosis is important for minimizing untoward outcomes.

Once considered a rare disease in children, it is now known that brucellosis may affect people of all ages, especially in regions where *Brucella melitensis* is the dominant species. The clinical course of illness and the risk of complications appear to be similar irrespective of the age of the patients. The true incidence of human brucellosis is unknown for most countries and no data are available for India. However, the disease may be encountered in significantly numbers in the rural populations of India, who often consume unpasteurized goat's/cow's milk.

EPIDEMIOLOGY

Children could be particularly at risk as they may adopt newborn or sick animals as pets. In some areas they may be the sole group presenting with acute symptoms, as adults are likely to be immune or chronically infected.

The severity and risk of disease are often determined by the type of *Brucella* to which an individual is exposed. *B. melitensis* (associated with sheep and goats) is the type most frequently reported as a cause of human disease and the most frequently isolated from cases. It is the most virulent type and associated with severe acute disease. *B. abortus* (associated with cattle) is the most widespread cause of infection, but associated with much less human disease. *B. suis* (associated with pigs) has a more restricted occurrence than *B. melitensis* and *B. abortus*. It is locally important as a source of human infection which can be as severe as that produced by *B. melitensis*. *B. canis* is a widespread infection of dogs in many countries. It is infrequently associated with human disease. Reported cases have been usually mild.

Although brucellosis in domesticated animals and the consequent transmission of infection to humans has been significantly decreased following the initiation of effective vaccination-based control and prevention programs in various parts of the world, it remains an uncontrolled problem in regions of high endemicity such as the Mediterranean, Middle East, Africa, Latin America and parts of Asia, including India.

Brucellosis is an important but neglected disease in India. Worldwide, the reported incidence of human brucellosis in endemic disease areas varies widely, from <0.01 to >200 per 100,000 population. However, several reports indicate that human brucellosis may be a fairly common disease in India. For example, a study from Bijapur by Mantur *et al* reported on 93 children with brucellosis who were identified by testing blood samples during a period of 13 years. The seroprevalence was 1.6% by serum agglutination test (SAT) (>1:160) and the diagnosis was confirmed in 43 of these pediatric patients by the isolation of *B. melitensis*. During the same period

a total of 492 adult patients were diagnosed with brucellosis at the same hospital indicating the importance of childhood brucellosis. Most of the pediatric patients were shepherds and the habit of consuming fresh goat milk and the close contacts with animals were the most likely risk factors contributing to infection.

ETIOLOGY

Brucellae are nonmotile, nonsporulating, nontoxigenic, non-fermenting, facultative, intracellular, gram-negative small coccobacilli parasites. *Brucella melitensis*, *B. suis*, *B. abortus*, and *B. canis* are the classic causative agents of disease in humans. Cattle, goats, sheep, and pigs are the main reservoirs of *Brucella*. Foodborne transmission is the major source of infection for most populations, with unpasteurized milk and cheese made from raw milk presenting the highest risk. Meat products less frequently lead to infection, since they are not usually eaten raw.

Transmission to humans may also occur through environmental or occupational contact with infected animal tissue and their discharges or from fetuses and placentae; or through direct contact of breaks in the skin and mucous membrane. Infected animals kept in populated areas or passing through close proximity to residential areas may produce heavy contamination of streets, yards or market places, especially if abortions occur in these animals. Inhalation brucellosis may then result from exposure to contaminated dust, dried dung, etc. Certain occupations such as farmers, farm laborers, animal attendants, slaughtermen, butchers, meat packers, dairy workers, shepherds, goatherds, pig keepers, laboratory technicians, veterinarians and inseminators are especially at risk.

Brucellosis may also present as a travel-associated disease. Blood or organ/tissue transfers are also potential sources of infection. Bone marrow transfer in particular carries a significant risk. However, it is known that person-to-person transmission is extremely rare. Occasional cases have been reported in which there was circumstantial evidence to suggest that close personal or sexual contact could be the possible route of transmission.

PATHOGENESIS

The major virulence factor of *Brucella* appears to be its cell wall lipopolysaccharide (LPS). *Brucellae* are intracellular microorganisms that survive and replicate within the reticuloendothelial (monocytes and macrophages) system. *Brucellae* are ingested by the macrophages and localized in the liver, spleen, bone marrow, and lymph nodes. They cause a granuloma formation in these organs. Strains containing smooth LPS are more virulent. Antibodies produced against the LPS antigen provide a means of diagnosis and provide long-term immunity. One of the major factors in recovery from infection is that sensitized T-lymphocytes release cytokines such as IFN- γ and TNF- α , which activate macrophages and increase their intracellular killing capacity.

CLINICAL FEATURES

Human brucellosis usually presents as an acute febrile illness. Most cases are caused by *B. melitensis*. All age groups are affected. It can be very difficult to diagnose in children without a history of food or animal exposure. The signs and symptoms are vague and not pathognomonic. Complications may affect any organ system.

The onset of symptoms may be acute or insidious. It is often a systemic infection characterized by continued, intermittent or irregular fever (often presenting as pyrexia of unknown origin), accompanied by nonspecific systemic symptoms such as headache, vomiting, weakness, sweating, chills, arthralgia, depression, weight loss, pharyngitis, generalized aching, refusal to feed or failure to thrive. Localized infections of organs, including the liver and spleen may be present. Physical findings are few and

include hepatosplenomegaly, arthritis or lymphadenopathy. In fact, most patients demonstrate the clinical triad of fever, arthralgia/arthritis and hepatosplenomegaly. Serious complications include meningitis, endocarditis and osteomyelitis.

COMPLICATIONS

Osteoarticular Complications

Bone and joint involvement are the most common complications of brucellosis, occurring in up to 40% of cases. Monoarticular arthritis of knee and hip in children is common. Sacroiliitis (especially common in adolescents), spondylitis, peripheral arthritis, osteomyelitis, bursitis, and tenosynovitis have been reported. Children often refuse to walk and bear weight on an extremity. Vertebral osteomyelitis has been reported; however paravertebral abscesses are uncommon.

Gastrointestinal Complications

B. melitensis infection is often foodborne, related to consumption of unpasteurized milk or dairy products. Foodborne brucellosis often resembles typhoid fever, since systemic symptoms predominate over gastrointestinal complaints. Still, some patients experience nausea, vomiting, and abdominal discomfort. Rarely ileitis, colitis and spontaneous bacterial peritonitis have been described.

Hepatobiliary Complications

Although the liver is commonly involved in brucellosis, liver function tests are often normal or only mildly elevated. Jaundice is very rare. Disease caused by *B. abortus* may show epithelioid granulomas resembling sarcoidosis. *B. melitensis* infection can cause scattered small foci of inflammation resembling viral hepatitis and rarely, areas of hepatocellular necrosis. Liver abscesses have been described in *B. suis* infections. Postnecrotic cirrhosis is extremely rare.

Pulmonary Complications

A spectrum of pulmonary complications have been described, including hilar or paratracheal lymphadenopathy, interstitial pneumonitis, bronchopneumonia, lung nodules, pleural effusions, and empyema.

Genitourinary Complications

Orchitis and epididymitis are the most common genitourinary complications of brucellosis in males. *Brucella* orchitis is unilateral and can mimic testicular cancer or tuberculosis. Renal involvement is rare. Rare cases of pelvic abscesses and salpingitis have been reported in females.

Cardiovascular Complications

Infective endocarditis is the most common cardiovascular manifestation, and it is reported to be the most common cause of death from brucellosis. Endocarditis is reported in about 2% of cases, and most commonly involves the aortic valve followed by the mitral valve.

Neurological Complications

Neurobrucellosis due to direct invasion of the central nervous system occurs in about 5% of cases of *B. melitensis* infection, leading to meningitis or meningoencephalitis. Headache, mental inattention and depression are common in neurobrucellosis. Other complications include cerebral vasculitis, mycotic aneurysms, brain abscesses, infarcts, hemorrhage, or cerebellar ataxia. Peripheral nerve complications include neuropathy, radiculopathy, Guillain-Barré syndrome, or Poliomyelitis-like syndrome.

Cutaneous Complications

These include rashes, nodules, papules and erythema nodosum. Cutaneous ulcers, abscesses, and suppurative lymphangitis have been reported. Occasionally, cutaneous purpura occur in association with severe thrombocytopenia, which has been ascribed to hypersplenism or hemophagocytic syndrome.

Ophthalmological Complications

Uveitis is the most frequent ophthalmic manifestation and is believed to be immunologically mediated. Steroids are the mainstay of treatment of this complication.

OTHER PRESENTATIONS

Brucellosis may also persist less commonly in the form of *chronic brucellosis* (whose clinical symptoms persist for 12 months or more from the time of the diagnosis); as relapse, chronic localized infection or delayed convalescence. Neonatal and congenital brucellosis has been rarely reported, resulting from transmission through transplacental routes, breastmilk and blood transfusions.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes other causes of fever of unknown origin and hepatosplenomegaly such as tuberculosis, malaria, enteric fever, rickettsial fever, leptospirosis, lymphomas, systemic lupus erythematosus and HIV infection. The presence of arthralgia/arthritis with hepatosplenomegaly, along with a history of consumption of unpasteurized milk or milk products, can help arrive at an early diagnosis.

Approach to Diagnosis

As per the case definition for brucellosis, the infection may be diagnosed if any of the following laboratory criteria is met:

- Isolation of *Brucella* from a clinical specimen;
- Four-fold or greater rise in *Brucella* agglutination titer between acute and convalescent phase serum collected greater than 2 weeks apart; and
- Demonstration by immunofluorescence of *Brucella* in a clinical specimen.

A definitive diagnosis can be established by isolating the organism from the blood, bone marrow or other tissues. It is essential to alert the laboratory that brucellosis is suspected, since isolation of the organism may take as long as 4 weeks from blood culture samples, unless lysis centrifugation method is used where results may be available in less than 5 days. The reported frequency of isolation from blood varies from less than 10–90%; *B. melitensis* is said to be more readily cultured than *B. abortus*. Bone marrow cultures are superior in yield as compared to blood cultures.

The tube serum agglutination test (SAT) remains the standard method. It measures the ability of serum to agglutinate killed organisms and reflects the presence of antilipopolysaccharide (LPS) antibody. Usage of the tube SAT test after treating serum with 2-mercaptoethanol to dissociate IgM into monomers helps in detecting IgG antibody; thereby helping in differentiating acute from chronic infections. A titer of 1:160 or higher is considered as diagnostic. To avoid the prozone effect, serum should be used in dilution of more than or equal to 1:320.

The Rose Bengal Test (RBT) is a commonly performed rapid screening test to detect antibodies against LPS, but the results should always be confirmed by other tests detecting agglutinating and nonagglutinating antibody and by culture results, especially in areas where there is a high prevalence of animal brucellosis.

Pancytopenia, anemia, thrombocytopenia or neutropenia may be detected in the peripheral smear in brucellosis, and may provide supportive evidence for diagnosis. Newer methods include

enzyme immunoassay (ELISA), which is however, less sensitive than SAT. Polymerase chain reactions (PCR) are also becoming increasingly available, and could be useful in neurobrucellosis where SAT often is negative.

MANAGEMENT

Brucellae demonstrate in vitro sensitivity to a number of oral antibiotics and to intravenous or intramuscular aminoglycosides. Therapy with a single antimicrobial drug has resulted in a high relapse rate; hence, combined regimens should be used. Nearly all patients also respond to a 6-week oral course with a combination of rifampin and doxycycline combination; fewer than 10% of patients relapse with this regimen. Doxycycline is overall the most effective antimicrobial agent, and when combined with an aminoglycoside, also offers low chance of relapse. Prolonged treatment (for at least 6 weeks) is the key to prevention of relapse.

The optimal treatment for brucellosis in children less than eight years of age has not been conclusively determined. Tetracyclines are contraindicated in this age group because of the potential for permanent staining of deciduous teeth and inhibition of bone growth. β -lactam antibiotics and third generation cephalosporins are not suitable for management of brucellosis since they lack intracellular killing activity, which is essential for eradication of the infection and prevention of relapse.

The recommendations for management of brucellosis in children are summarized in **Box 1**. The onset of therapy may be accompanied by a Jarisch-Herxheimer type of reaction, possibly due to a high antigen load. This may be rarely severe enough to merit steroid therapy.

BOX 1 Treatment of brucellosis

1. For children ≥ 8 years:

First line regimen: Doxycycline (2–4 mg/kg/day; maximum 200 mg/day) orally for 6 weeks PLUS rifampicin (15–20 mg/kg/day; maximum 600–900 mg/day) orally for 6 weeks

Alternative therapy: Doxycycline (2–4 mg/kg/day; maximum 200 mg/day) orally for 6 weeks PLUS streptomycin (15–30 mg/kg/day; maximum 1g/day; IM) for 2 weeks or gentamicin (3–5 mg/kg/day; IM/IV) for 2 weeks

2. For children < 8 years:

Trimethoprim-Sulfamethoxazole (trimethoprim 10 mg/kg/day; sulfamethoxazole 50 mg/kg/day) [maximum dose of trimethoprim 480 mg/day] PLUS rifampicin (15–20 mg/kg/day; maximum 600–900 mg/day) for 6 weeks

3. For children with endocarditis, osteomyelitis and meningitis:

Doxycycline (2–4 mg/kg/day; maximum 200 mg/day) for 4–6 months orally PLUS gentamicin (3–5 mg/kg/day; IV) for 2 weeks PLUS rifampicin (15–20 mg/kg/day; maximum 600–mg/day) orally for 4–6 months

Infected valves in patients with endocarditis may need to be replaced early in therapy.

OUTCOME

Before the advent of specific antimicrobial agents, the course of brucellosis was often prolonged and deaths were known. Since the institution of specific antibiotics, deaths are rare and known to occur in the presence of complications such as neurobrucellosis or endocarditis. Even in these conditions, death rates are low with prolonged antibiotic therapy for 6 months.

PREVENTION

Preventive strategies depend on eradication of the organism from cattle, goats, sheep and pigs. Pasteurization of milk and milk

products is an important aspect of prevention. Consumption of raw unpasteurized milk and milk products from potentially infected cows, goats, and sheep or direct contact with infected animal body fluids or products of conception should be discouraged. Farmers, hunters and animal handlers should be educated about the proper handling of carcasses such as using protective clothing and gloves and when handling potentially infected material and to bury the remains. Safe and effective vaccines for the prevention of human brucellosis are not generally available.

IN A NUTSHELL

1. Human brucellosis usually presents as an acute febrile illness. It affects all ages.
2. Most cases are caused by *B. melitensis*.
3. Complications can affect any organ system. Joint involvement may be seen in up to 40% of cases. Infective endocarditis and neurobrucellosis are rare but serious complications.
4. Brucellosis may persist as relapse, chronic localized infection or delayed convalescence.
5. Cattle, sheep, goats and pigs are the principal reservoirs of *Brucella*.
6. Transmission to humans occurs through occupational or environmental contact with infected animals or their products. Foodborne transmission is the main source of infection, with cheese made from raw milk and unpasteurized milk presenting the highest risk.
7. In acute brucellosis, isolation of *Brucella* from blood, bone marrow or other tissues is confirmatory.
8. Serum agglutination test (SAT) is the most useful serological test, and titres of 1:160 or higher are considered as positive. Culture is often negative, especially in long-standing disease.
9. The essential principle in the management of all forms of human brucellosis is the administration of effective antimicrobial agents for an extended period of time.
10. For children more than 8 years of age, doxycycline plus rifampicin for 6 weeks is the first line regimen, while for children less than 8 years of age, trimethoprim-sulfamethoxazole with rifampicin for at least 6 weeks is the treatment of choice.

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Chapter 29.17

Relapsing Fever

P Ramachandran

Relapsing fever is a zoonotic arthropod-borne infection caused by the spirochetes of *Borrelia* species characterized by recurrent cycles of pyrexia which are separated by intervals of apparent recovery. Based on the vector responsible, it can be tick-borne relapsing fever (TBRF) or louse-borne relapsing fever (LBRF). TBRF is reported all over the world though only sporadic cases are reported from India. Outbreak of LBRF occurs in the refugee camps of war and famine affected African countries. There is a paucity of information about relapsing fever in India.

EPIDEMIOLOGY

Tick-borne relapsing fever is found in discrete areas throughout the world, including mountainous areas of North America, plateau regions of Mexico, Central and South America, the Mediterranean, Central Asia, and much of Africa. LBRF causes sporadic illness and outbreaks in sub-Saharan Africa, particularly in regions affected by war and in refugee camps. LBRF is commonly found in Ethiopia, Sudan, Eritrea, and Somalia. Illness can be severe, with mortality rate of 30–70% in outbreaks.

ETIOLOGY

Relapsing fever is caused by spirochetes of *Borrelia* species and transmitted by arthropods (ticks or lice). TBRF is caused by many species of *Borrelia* while LBRF is caused by only *Borrelia recurrentis*. In North India, TBRF is spread by *Ornithodoros tholozani*, *Ornithodoros crossi*, *Ornithodoros lahorensis* and the fowl tick *Argas persicus*. TBRF is a zoonosis and is enzootic in many countries. It is spread by multiple tick species, each of which has a preferred habitat and set of hosts. *Borrelia* that cause TBRF are transmitted to humans through the bite of infected *soft ticks* of the genus *Ornithodoros*. They live within rodent burrows, feeding as needed on the rodent as it sleeps. Humans typically come into contact with soft ticks when they sleep in rodent-infested cabins mostly in summer months while vacationing. Rodents and other animals serve as natural reservoirs. TBRF is acquired directly through the tick bite, usually from saliva secreted by the tick into the skin.

Louse-borne relapsing fever is principally a disease seen in the developing world; it is spread from person to person by the body louse *Pediculus humanus corporis*, which only feeds on humans and lives on clothing. Humans are probably the only reservoir of *B. recurrentis*. LBRF can occur in epidemics, including large ones involving millions of people generally in refugee settings. LBRF outbreaks most commonly occur in conditions of overcrowding and social disruption. LBRF is acquired when people crush a louse with their fingers; the organism is introduced at the bite-site, into the skin of the crushing fingers, or into the conjunctivae when they rub their eyes.

PATHOGENESIS

Spirochetes causing relapsing fever have a unique process of DNA rearrangement that allows them to periodically change the molecules on their outer surface. This process, called antigenic variation, allows the spirochete to evade the host immune system and causes relapsing episodes of fever and other symptoms. These variable proteins determine differences in disease expression. For example, propensity for invasion of the central nervous system with *Borrelia turicatae* infection is determined by variability in a single surface protein of the bacterium.

CLINICAL FEATURES

The incubation period for clinical illness from the bite is 5–10 days. Relapsing fever is characterized by episodes of sudden onset of high fever which may be as high as 43°C and is usually above 39°C lasting for 2–9 days, followed by afebrile periods of about 7 days, followed by another episode of fever (**Fig. 1**). This process can recur from 3 to 10 times. Duration of fever during febrile phase is shorter in TBRF compared LBRF. Along with fever, patients may experience generalized bodyache, muscle pain, joint pain, headache, nausea, vomiting, anorexia, dry cough, rash, neck pain, eye pain, confusion and dizziness (**Table 1**). During the end of the primary febrile episode, a diffuse, erythematous, macular, or petechial rash lasting up to 2 days can develop over the trunk and shoulders.

Each febrile episode ends with a *crisis*. During the *chill phase* of the crisis, patients develop very high fever (up to 106.7°F or 41.5°C) with rigors and may become delirious, agitated, hypertensive, and develop tachycardia and tachypnea lasting for 10–30 min. This phase is followed by the *flush phase*, characterized by drenching sweats and a rapid decrease in body temperature and transient hypotension. This phase usually persists for several hours. Overall, patients who are not treated will experience recurrent episodes of fever before illness resolves. On physical examination, there are no findings specific for TBRF. Patients typically appear moderately ill and may be dehydrated. Splenomegaly, which the patient can experience as abdominal or left shoulder pain, and hepatomegaly can occur in both LBRF and TBRF. Less frequently, patients may have jaundice, meningismus, and photophobia (**Table 1**).

Acute respiratory distress syndrome may occur in TBRF. Localizing neurologic symptoms, including hemiplegia, facial palsy, myelitis, and radiculopathy are more common in TBRF. Epistaxis, petechiae, and ecchymoses are common in LBRF.

Tick bite

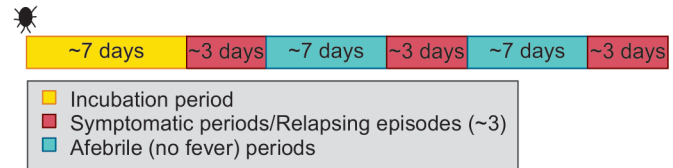


Figure 1 Timeline of relapsing fever

Source: Centers for Disease Control, Atlanta, USA

Table 1 Symptoms and signs among patients with tick-borne relapsing fever

Symptom	Frequency of symptom	Sign	Frequency of sign
Headache	94%	Confusion	38%
Myalgia	92%	Rash	18%
Chills	88%	Jaundice	10%
Nausea	76%	Hepatomegaly	10%
Arthralgia	73%	Splenomegaly	6%
Vomiting	71%	Conjunctival injection	5%
Abdominal pain	44%	Eschar	2%
Dry cough	27%	Meningitis	2%
Eye pain	26%	Nuchal rigidity	2%
Diarrhea	25%		
Photophobia	25%		
Neck pain	24%		

Source: Centers for Disease Control, Atlanta, USA

Myocarditis can occur in both LBRF and TBRF. Delirium or apathy and occasionally stupor or coma also can occur in both forms.

Malaria, influenza, typhoid fever, brucellosis, rickettsioses, dengue, leptospirosis, rat-bite fever, meningococcemia and viral hepatitis should be considered in the differential diagnosis.

Mortality from untreated relapsing fever is most common during the crisis and its immediate aftermath and is usually associated with myocarditis, hepatic failure or disseminated intravascular coagulation.

LABORATORY DIAGNOSIS

The definitive diagnosis of TBRF is based on the observation of *Borrelia* spirochetes in peripheral blood, bone marrow, or cerebrospinal fluid in a symptomatic person (Fig. 2). It is best visualized by dark field microscopy of peripheral blood, but can also be detected in thin smear or thick smear using Wright-Giemsa or acridine orange stains. The organisms are best detected in blood obtained while a person is febrile. With subsequent febrile episodes, the number of circulating spirochetes decreases, making it harder to detect. Even during the initial episode spirochetes will only be seen 70% of the time.

Blood samples obtained before antibiotic treatment can be cultured using Barbour-Stoner-Kelly (BSK) medium or by inoculating immature mice. The spirochete will usually be evident within 24 hours if the blood was drawn during a febrile episode. The polymerase chain reaction (PCR) is useful for identifying the infecting species. These are done only in reference labs.

Serologic testing is not useful for immediate diagnosis. To confirm the diagnosis of TBRF, *Borrelia* specific antibody titers should increase 4-fold between acute and convalescent serum samples. The rise in antibody titer may be blunted by early antibiotic therapy. Serologic testing for TBRF is not standardized and results vary by laboratory.

Nonspecific laboratory findings include normal to increased white blood cell count with a left shift, a mildly increased serum bilirubin level, mild to moderate thrombocytopenia, elevated erythrocyte sedimentation rate (ESR), and slightly prolonged prothrombin time (PT) and partial thromboplastin time (PTT). The electrocardiogram may reveal a prolonged QTc interval in patients with myocarditis. Some such patients have cardiomegaly and pulmonary edema on chest radiograph. Analysis of the

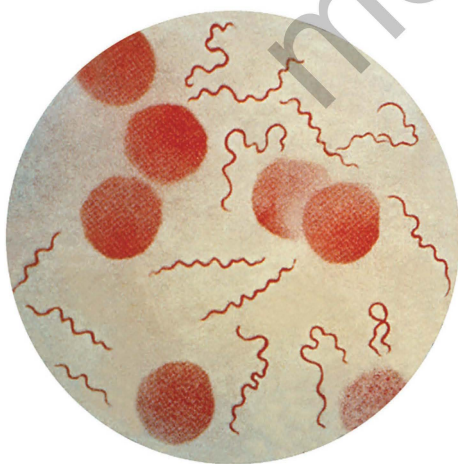


Figure 2 Photomicrograph revealing the presence of numerous *Borrelia recurrentis* bacteria, which cause European relapsing fever. This bacterium is transmitted from person-to-person by way of the human body louse, *Pediculus humanus* var. *corporis*.

Source: PHIL, Centers for Disease Control, Atlanta, USA.

cerebrospinal fluid (CSF) is indicated when there are signs of meningitis or meningoencephalitis. The presence of pleocytosis and/or mildly to moderately elevated protein levels in the CSF requires intravenous antibiotic therapy.

TREATMENT

Tick-borne relapsing fever spirochetes are susceptible to penicillin and other beta-lactam antimicrobials, as well as tetracyclines and macrolides. Oral or parenteral tetracycline is the drug of choice for LBRF and TBRF. In TBRF for children above 8 years of age and young adults, tetracycline 500 mg or 12.5 mg/kg PO every 6 hours or doxycycline 100 mg or 2.5 mg/kg PO every 12 hours for 10 days is effective. For children below or equal to 8 years of age erythromycin 12.5 mg/kg every 6 hours for 10 days is effective.

In contrast to TBRF, LBRF caused by *B. recurrentis* can be treated effectively with a single dose of antibiotics. Doses for children are oral tetracycline at 12.5 mg/kg, oral doxycycline at 5 mg/kg, and intramuscular penicillin G procaine at 200,000–400,000 units. For children above 8 years of age and adults, a single dose of oral tetracycline 500 mg, oral doxycycline 200 mg or intramuscular penicillin G procaine 400,000–800,000 units is effective. Alternative is oral erythromycin, 500 mg for adults and 12.5 mg/kg for children. Intravenous penicillin G or ceftriaxone for 10–14 days is effective treatment for CNS involvement.

When initiating antibiotic therapy, all patients should be observed during the first 4 hours of treatment for a Jarisch-Herxheimer reaction. The reaction, a worsening of symptoms with rigors, hypotension, and high fever, occurs in over 50% of cases and may be difficult to distinguish from a febrile crisis. Supportive care is required for the symptoms. Features associated with a poor prognosis are, stupor or coma on admission, diffuse bleeding, myocarditis, poor hepatic function, bronchopneumonia, coinfection with typhus, typhoid or malaria. In addition acute respiratory distress syndrome requiring ventilatory support has been described in TBRF.

COMPLICATIONS AND PROGNOSIS

Given appropriate treatment, most patients recover within a few days. The mortality rates for untreated LBRF and TBRF are in the ranges of 10–70% and 4–10%, respectively. With prompt treatment with appropriate antibiotics, the death rate for LBRF is 2–5% and for TBRF is less than 2%. Long-term sequelae of TBRF are rare but include iritis, uveitis, cranial nerve involvement, and other neuropathies.

TICK-BORNE RELAPSING FEVER IN PREGNANCY

Tick-borne relapsing fever contracted during pregnancy can cause spontaneous abortion, premature birth, low-birthweight and neonatal death. The maternal-fetal transmission of *Borrelia* is believed to occur either transplacentally or while traversing the birth canal. In general, pregnant women have higher spirochete loads and more severe symptoms than nonpregnant women.

PREVENTION

The risk for tick-borne disease can be minimized in endemic areas by maintaining rodent-free dwellings. Ticks can be destroyed by spraying with lindane 1% (gamma benzene hexachloride). Visitors to infected areas should wear protective clothing and use insect repellants. Ticks should be looked for and removed mechanically from the body before going to bed after the day's work. Giving prophylactic doxycycline for 4 days after a tick bite has been shown to prevent TBRF. LBRF can be prevented by lowering the risk of louse infestation through improved personal hygiene, reduction of crowding and better access to washing facilities.

IN A NUTSHELL

1. Relapsing fever is a zoonotic arthropod-borne infection caused by the spirochetes of *Borrelia* species.
2. The two major forms of the disease are tick-borne relapsing fever (TBRF) or louse-borne relapsing fever (LBRF).
3. TBRF is seen throughout the world while LBRF is seen mainly in Sub-Saharan Africa. Sporadic cases of TBRF are reported in India.
4. Relapsing fever is characterized by episodes of high-grade fever with other constitutional symptoms followed by afebrile periods and this cycle recurs for 3–10 times.
5. Spirochetes causing relapsing fever periodically change the molecules on their outer surface and this antigenic variation allows the spirochete to evade the host immune system and causes relapsing episodes.
6. The other characteristic of the febrile episodes are that they end with a *chill phase* of 10–30 minutes of high fever, rigors, tachycardia and tachypnea and a *flush phase* of several hours characterized by marked sweating, sudden decrease in temperature and transient hypotension.
7. Fatal complications, such as myocarditis, acute liver failure, ARDS, DIC and meningoencephalitis, can occur in untreated cases.
8. Diagnosis depends on demonstration of spirochetes by dark-field microscopy or in thin or thick blood smears stained with Giemsa or Wright's stain.
9. For TBRF in children above 8 years of age and adults, tetracycline or doxycycline for 10 days is the preferred treatment. For children below or equal to 8 years of age erythromycin for 10 days is the preferred regimen. For LBRF these drugs are given as a single dose. For neurologic complications intravenous penicillin or ceftriaxone is indicated.
10. Mortality is high in untreated cases especially LBRF.

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Chapter 29.18

Lyme Disease

P Ramachandran

Lyme disease derives its name from the town *Lyme* in Connecticut, America, where it was first recognized in 1977. Lyme disease is focally endemic in temperate zones of North America, Europe and Asia. Sporadic cases are reported in India with skin, eye and neurologic manifestations. It is a tick-borne spirochetal infection.

ETIOLOGY

The members of *Borrelia* species are spirochetes, which are motile, spiral, or wavy bacteria. Infection occurs through the bite of infected ticks, both adults and nymphs, of the genus *Ixodes*. Three species of *Borrelia* account for most cases of Lyme disease in the world: *Borrelia burgdorferi* causes Lyme disease in North America and less extensively in Europe. In Europe and Asia, *Borrelia afzelii* and *Borrelia garinii* are the predominant species. In Asia, *B. afzelii* and *B. garinii* are thought to be the most common causes of Lyme disease. However, *B. burgdorferi* has also been detected from a skin lesion of a patient with Lyme disease in Taiwan. Biological differences among the three predominant *Borrelia* species are likely to be responsible for some of the differences in clinical manifestations. The lifecycle of *B. burgdorferi* requires a tick host and a mammalian host. *B. afzelii* is mainly associated with rodents as reservoirs, whereas *B. garinii* is mainly associated with birds as reservoir.

PATHOGENESIS

B. burgdorferi is deposited in skin during tick feeding. After inoculation into the skin, *Borrelia* begins to multiply rapidly. *Borrelia* species do not produce potent toxins, but cause illness by migrating through tissues, disseminating in the blood, adhering to host cells, and producing immunologic response. Dissemination to distant sites begins to occur within two to three days. The spirochete adheres to the surfaces of a wide variety of different types of cells, but the principal target organs are skin, central and peripheral nervous system, joints, heart, and eyes. The symptoms of disseminated Lyme disease are due to inflammation mediated by interleukin 1 and other lymphokines in response to the presence of the organisms. During untreated late stage infection in mammals, symptoms persist at specific sites like joints, central nervous system (CNS) and it is suspected that *B. burgdorferi* may persist at low levels in these tissues.

CLINICAL FEATURES

There are three stages of Lyme disease:

Early Localized Disease (Stage 1)

Clinical features are similar to flu such as fever, headache, tiredness, neck pain, arthralgia or myalgia. A flat or slightly raised red spot called erythema migrans (EM) appears at the site of the tick bite with a clear area in the center (bull's eye rash) (**Fig. 1**). Without treatment, it can last 4 weeks or more (**Table 1**). It is usually a painless rash that appears within 7–14 days after the bite (range 3–30 days). The absence of a recognized tick bite does not exclude Lyme disease, as long as exposure to tick bite in an endemic area is a possibility. Untreated, the rash expands over the course of days to weeks to form a large, annular, erythematous lesion that is at least 5 cm and as much as 70 cm in diameter (median 15 cm). The lesions are seen commonly over the head and neck in younger children

and arms and lower limbs in older children. It may also be seen over back and other areas. Though a central clearing of rash is mentioned as a typical feature, in most cases it is uniformly erythematous.

Early Disseminated Disease (Stage 2) (Table 1)

Multiple erythema migrans, cranial nerve palsy, meningitis and carditis are the clinical manifestation of this stage which may occur days to weeks after the tick bite. *Multiple erythema migrans* is a pathognomonic feature in endemic areas. Cranial nerve palsy usually involves facial nerve as unilateral or sometimes bilateral facial palsy. Meningitis is manifested by headache, nuchal rigidity and papilledema. Lyme meningitis in children is frequently associated with increased intra cranial pressure which may lead to transient or permanent loss of vision. Carditis manifests with I or II degree or complete heart block, rarely with myocarditis or left ventricular dysfunction. Systemic signs and symptoms, such as fever, fatigue, headache, and arthralgia are common in this stage of Lyme disease.

Late Disease (Stage 3)

Late disease presents weeks or months after primary infection if not treated adequately. Arthritis is the most common manifestation of late Lyme disease (**Table 1**). There is a wide variability in the severity of Lyme arthritis. The arthritis is usually monoarticular or oligoarticular and affects the large joints, particularly the knee, which is involved in more than 90% of cases. Many present with migratory



Figure 1 Erythema migrans with central clearing (bull's eye)
(Courtesy: James Gathany, PHIL, CDC, USA)

Table 1 Clinical stages of Lyme disease

Stage	Duration after tick bite	Clinical features
Stage 1	3–30 days	Erythema migrans (single), variable constitutional symptoms (headache, fever, myalgia, arthralgia, fatigue)
Stage 2	4–12 weeks	Multiple erythema migrans, cranial neuritis (commonly facial nerve), meningitis, papilledema, carditis (heart block), ocular disease; constitutional symptoms common
Stage 3	Above 8 weeks	Mono or oligoarthritis mainly involving knee; resolve and recur to involve multiple joints

arthritis. In some instances it may be confused with acute bacterial arthritis. The differentiating features are, children with Lyme arthritis can bear weight and walk and fever is not an associated feature. The arthritis may slowly resolve and may recur to involve multiple joints. Long-term prognosis of Lyme arthritis in children is excellent.

DIAGNOSIS

The diagnosis of early Lyme disease should be made on clinical grounds alone when a characteristic EM lesion is present in a patient who lives in or has recently traveled to an endemic area. EM initially can be confused with nummular eczema, tinea corporis or granuloma annulare. The relatively rapid expansion of EM helps to distinguish it from these other skin lesions. The clinical manifestation of arthritis of late stage is sometimes confused with a septic arthritis or other causes of arthritis in children, such as juvenile rheumatoid arthritis or rheumatic fever. The facial nerve palsy due to Lyme disease is clinically indistinguishable from idiopathic Bell's palsy, although bilateral involvement is much more common with Lyme disease.

Immunoglobulin (Ig) M antibodies to *B. burgdorferi* typically appear in 3–4 weeks. IgG antibodies appear in 4–8 weeks and peak at 4–6 months. Serology is likely to be negative in early localized stage (stage 1). In early disseminated Lyme disease (stage 2) serologic tests are usually positive for both IgM and IgG antibodies. In late disease (Lyme arthritis), serologic tests should be positive for IgG antibodies. Both IgM and IgG antibodies may remain elevated despite successful antibiotic therapy and complete resolution of symptoms.

When serologic testing is indicated, a two-tier testing is recommended. Initially an enzyme-linked immunosorbent assay (ELISA) followed by a Western blot are the tests of choice. This two-tier testing is recommended because of its high degree of sensitivity and specificity compared to a single test. Polymerase chain reaction (PCR) test has some usefulness when done in synovial fluid in arthritis cases, but not useful in cerebrospinal fluid due to high false positivity.

TREATMENT

The goal of therapy is to shorten the duration of the early disease and to reduce the risk of development of late Lyme disease. *B. burgdorferi* is highly susceptible to beta-lactam antibiotics and tetracyclines. They are of equivalent choice for treatment for early Lyme disease, doxycycline for above 8 years and amoxicillin for less than 8 years of age. Of the oral agents, doxycycline has the best penetration into the CNS. Doxycycline is not recommended for children under the age of 8 years or for pregnant or lactating women. However, a single treatment course of doxycycline may be given to children younger than 8 years in whom the alternate agents are contraindicated. The doses and duration are listed in **Box 1**.

BOX 1 Recommended treatment of Lyme disease

Drug and doses

1. Amoxicillin 50 mg/kg/day PO in 3 divided doses
2. Doxycycline 4 mg/kg/day PO in 2 divided doses
3. Cefuroxime 30 mg/kg/day PO in 2 divided doses (max 1,000 mg/day)
4. Ceftriaxone 50–75 mg/kg/day IV OD

Duration of therapy: 2–3 weeks for cardiac disease, erythema migrans, and cranial neuritis; up to 4 weeks for meningitis and arthritis. Carditis and meningitis should preferably be treated with injectable drugs.

Response to Therapy

Majority of patients with early Lyme disease who receive appropriate antibiotic therapy have complete resolution of the signs and symptoms of infection within 20 days. Patients who have systemic illness at the beginning of treatment may take longer to recover. In addition, appropriate dosing and duration of therapy early in the course (i.e., within weeks of the onset of infection) prevents progression to late Lyme disease. Infectious Diseases Society of America (IDSA) guidelines 2006 recommend parenteral therapy with ceftriaxone when abnormal CSF findings are present (**Box 1**). Patients with isolated facial nerve palsy in the absence of meningitis are treated with oral doxycycline.

PREVENTION

Personal protection against tick bites is useful by application of tick repellents, such as diethyl-3-methylbenzamide (DEET), on skin and permethrin on clothing. Promptly removing ticks after exposure to tick habitat also will reduce the infection risk to some extent.

IN A NUTSHELL

1. Lyme disease (Lyme borreliosis) is a spirochetal infection caused by *Borrelia* species and transmitted by tick. Borreliosis involving eye, skin and nervous system have been reported from India.
2. The hall mark of early localized disease is erythema migrans. This stage lasts for about 4 weeks.
3. Early disseminated disease (the second stage) starts after about 4 weeks of tick bite. It is characterized by multiple erythema migrans, cranial neuritis (facial palsy-unilateral or bilateral), myocarditis, and eye involvement. This stage lasts up to 3 months.
4. In the third stage (late disease) arthritis is the hall mark. It starts after about 2 months of onset with mono/oligoarthritis and later recur involving multiple joints. Complete resolution occurs.
5. The diagnosis of early localized disease is only clinical with the presence of erythema migrans and antibodies are usually not present in this stage. IgM and IgG antibodies are present in the second stage while IgG antibodies are seen in the third stage.
6. Beta-lactam antibiotics like amoxicillin are given for children equal to or below 8 years of age, while doxycycline is preferred for children above 8 years of age. For CNS involvement intravenous ceftriaxone is the drug of choice.

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Chapter 29.19

Nocardiosis

Subhasish Bhattacharyya

Nocardiae are found in environment, notably in soil and over 30 species have been showed to be associated with opportunistic disease in human, termed as Nocardiosis, which includes acute, sub-acute or chronic suppurative infections with a tendency for remission and exacerbations. Principal causes of the disease are *Nocardia asteroides* (including *Nocardia cyriacigeorgica*) so named because of their star-shaped colonies. Other causes of the disease are *Nocardia farcinica*, *Nocardia brasiliensis*, *Nocardia abscessus*, *Nocardia otitidiscaviarum*, *Nocardia nova* and *Nocardia transvalensis*. *N. brasiliensis* infections are often limited to skin and subcutaneous tissue and all other species have been reported in pulmonary and systemic infections.

MICROBIOLOGY

The family *Nocardiaceae* is composed of aerobic actinomycetes and characterized by filamentous growth with true branching, are catalase and urease positive and grow on multiple media including Lowenstein-Jensen medium, brain-heart infusion agar, simple blood agar and sabouraud dextrose agar. They grow best at 37°C in presence of 10% carbon-dioxide. It takes 2–4 weeks to recognize the morphologic characteristics of the colony. Laboratory personnel should be notified to observe this culture for at least 4 weeks, when nocardiosis is considered. Many *Nocardia* are acid fast, so a modified Ziehl-Neelsen or Kinyoun stain with 1% sulfuric acid decolorization is best for demonstrating *Nocardia*. *Nocardia asteroides* is the most common and *N. brasiliensis* is the second most frequent etiologic agent of human nocardiasis.

EPIDEMIOLOGY

Nocardia are ubiquitous saprophytic soil organism usually found in house dust, garden soil, fresh water, decaying vegetation and swimming pools. The lung is the primary portal of entry of nocardiosis. Nearly all cases are sporadic, but outbreaks have been associated with contamination of hospital environment, solutions or drug injection equipment. Person to person spread is rare, there is no seasonality, risk of pulmonary and disseminated disease is greater than usual among the people with deficient cell-mediated immunity, lymphoma, lymphoreticular malignancy, Chronic obstructive pulmonary disease (COPD), transplantation, AIDS (< 250 CD4 + T-lymphocytes/ μ L), glucocorticoid therapy. Incidence increases up to 140 folds greater among the patients with AIDS and nearly 340 folds greater among the bone marrow recipient than the general population. It is also associated with tuberculosis, chronic granulomatous disease and treatment with monoclonal antibodies to tumor necrosis factor (infliximab). Any child with nocardiosis and known cause of immunosuppression should undergo tests to determine adequacy of the phagocytic respiratory burst. This infection mostly occurs in tropical and subtropical regions especially in Southeast Asia and India, and the most important risk factor is frequent contact with soil or vegetable matter.

PATHOGENESIS

Infection usually occurs by inhalation of bacilli or occasionally by traumatic inoculation into the skin following arthropod and cat bites. Characteristic histologic feature of nocardiosis is an abscess with extensive neutrophil infiltration and prominent necrosis

without extensive fibrosis, granulomatous inflammation or encapsulation. It survives within the phagocytes by neutralization of oxidants, prevention of phagosome lysosome fusion and prevention of phagosome acidification. Neutrophil do not kill them efficiently. Nocardiosis produces suppurative necrosis and abscess formation similar to that seen in pyogenic infection. Disseminated infection occurs via hematogenous spread, especially in immunocompromised host. Keratitis, either post traumatic or associated with contact lens use and endophthalmitis have been reported.

CLINICAL MANIFESTATIONS

Pulmonary nocardiosis, the most common form of nocardial disease in the respiratory tract occurring in more than two-third cases, causes acute, subacute or chronic suppurative disease. Pulmonary infection can manifest with dyspnea along with anorexia and weight loss. Cough is prominent and produces thick, purulent nonmalodorous sputum, hemoptysis is rare. Chronic pulmonary nocardiosis is much like tuberculosis. Widespread dissemination can occur specially in solid-organ transplant recipients and immunocompromised hosts.

Central nervous system is most common secondary site, where disease manifest as single or multiple brain abscesses, usually supratentorial and often multiloculated. *N. farcinica* and *N. otitidiscaviarum* mostly associated with brain abscess which may have implications for treatment due to their antibiotic resistance pattern. *Nocardia* also has been associated with persistence neutrophilic meningitis, despite negative routine culture. Neurotropism is so prominent a feature of nocardiosis that cranial CT and MRI imaging should be performed in patients with pulmonary infection even without symptoms of CNS disease. Imaging typically shows a necrotic cavity surrounded by contrast-enhancing smooth capsule of uniform thickness and surrounding edema, in contrast to more irregular capsule seen in malignant tumors. MRI T₂—weighted image may show multiple concentric rings with varying signal intensities.

Skin manifestations (third most commonly involved organ) include cellulitis, pustules, pyoderma, ulcerations, subcutaneous abscess and mycetoma. Patient with skin involvement should be evaluated to exclude disseminated disease. *Nocardia* can disseminate to almost any organ like kidney (fourth most common site), intestine, liver, spleen, joints, bones and adrenal glands. Renal manifestations are dysuria, hematuria and pyuria.

DIAGNOSIS

Sputum or pus examination shows crooked, branching, beaded, gram-positive weak acid-fast filaments (by modified Kinyoun, Ziehl-Neelsen method). *Nocardiae* grow relatively slowly; develop characteristic appearance till 4 weeks. Laboratory should be alerted when nocardiosis is suspected in order to maximize the isolation.

TREATMENT

Sulfonamides are the drug of choice for nocardiosis. The combination of sulfamethoxazole (SMX) and trimethoprim (TMP) is probably equivalent to sulfonamides that may be more effective. At the outset, 10–20 mg/kg of TMP and 50–100 mg/kg of SMX should be given each day in two divided doses and later daily dose can be decreased. Importantly, thrice weekly TMP-SMX used for *Pneumocystis jirovecii* infection prophylaxis, is ineffective in preventing nocardiosis. Duration of the treatment varies from 6–12 months depending upon the clinical manifestations and host defenses. TMP-SMX resistance range from 20% for *N. brasiliensis* to 80% for *N. farcinica*. Linezolid is the only antibiotic to which 100% of the isolates are susceptible. Resistance among all stains tested is

lowest for amikacin (5%), which is best established parenteral drug and is given in a dose of 5–7.5 mg/kg every 12 hourly. TMP-SMX with amikacin combination should be used for progressive disease especially in immunocompromised host. Mortality ranges from 15% to 26%; the factor that increases mortality includes concurrent corticosteroid or antineoplastic therapy and cytomegalovirus coinfection. Consideration of nocardial infection in a differential diagnosis of immunocompromised or debilitated patient should be considered for earlier diagnosis and improved outcome. Despite appropriate therapy, the overall mortality rate is more than 50%, may be due to delayed diagnosis.

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IN A NUTSHELL

1. *Nocardia* is a ubiquitous soil organism.
2. Most infections occur in children with HIV infection and immunodeficiency, chronic high dose corticosteroid therapy, lymphoreticular malignancies, organ transplantations.
3. Pulmonary disease occurs in more than two-third of cases; disseminated disease involves CNS and any other organ.
4. Cutaneous and lymphocutaneous nocardiosis are due to direct inoculation.
5. Laboratory personnel should be notified to hold the culture at least for 2 weeks to allow the slow growth of *Nocardia*.
6. TMP-SMX is the treatment of choice. Other agents include linezolid, amikacin and ceftriaxone. Duration of therapy for invasive disease is 6–12 months or more.

Chapter 29.20

Actinomycosis

Subhasish Bhattacharyya

Actinomycosis is a slowly progressive infection caused by anaerobic or microaerophilic filamentous, branching, gram-positive, nonspore forming, catalase-negative bacilli. It is a chronic granulomatous, suppurative disease, characterized by extension to contiguous tissue with the formation of numerous draining fistulas and sinuses. On Gram stain, *Actinomyces* cannot be distinguished from *Nocardia*, which grows aerobically and stain with modified acid-fast technique but *Actinomyces* species do not. *Actinomyces Israelii* is the predominant species causing disease. Most infections are polymicrobial, involving other anaerobic and aerobic bacteria. Comparative 16S rRNA gene sequencing has led to the identification of expanding list of *Actinomyces* spp.

EPIDEMIOLOGY

Actinomyces has no geographical boundaries. Mucosal disruption may lead to infection at virtually any site of the body. Actinomycosis has been called most misdiagnosed disease, is often missed by experienced clinicians. *Actinomyces* species colonize the oral cavity (carious teeth, dental plaque and tonsillar crypts) prevalence rate increasing from 31% to 97% within the first two years of life.

PATHOGENESIS

Actinomyces species generally have low virulence. A critical step in the development of Actinomycosis is disruption of mucosal barrier, infection (herpes simplex, cytomegalovirus infection), trauma, and surgical injury of mucous membrane. Pulmonary infections usually follow aspiration of secretions. Once established it spreads continuously in a slow progressive manner, ignoring tissue planes, producing characteristic chronic, indolent single or multiple indurations with central necrosis consisting of neutrophils and sulfur granules with fibrotic wall. Over time, sinus tracks to skin and adjacent organs to bone may develop. Some features of this disease may mimic malignancy. Immunodeficiency, HIV infection, radio- or chemotherapy and transplantation facilitate the development of actinomycosis. Patient with chronic granulomatous disease have an unusual susceptibility to *Actinomyces* infection.

CLINICAL MANIFESTATIONS

Actinomyces occur most frequently at an oral, cervical or facial site (generally at the angle of the jaw, "lumpy jaw") often mistaken for neoplasm. Classically, small abscess form at the site of origin, with an extension to form multiple sinus tracks that can drain yellow, gritty, purulent material (sulfur granules). Contagious extension to the cranium, cervical spine, or thorax is potential sequelae. Fever or systemic illness is usually absent. Appendix is the most frequent gastrointestinal site and appendicitis with perforation is the most common predisposing event. Chronic nonspecific symptoms consisting of fever, chills, weight loss, diarrhea, constipation, abdominal pain may present and mimic tuberculosis or lymphoreticular malignancy. It must be differentiated from tuberculosis, nocardiosis and fungal infection. Sinus tracts to the abdominal wall, to the perianal region or between the bowel and other organs may develop and mimic inflammatory bowel disease. Thoracic actinomycosis presents with chronic indolent and slowly progressing pneumonia with or without plural involvement, also may mimic tuberculosis, lung abscess and nocardiosis.

DIAGNOSIS

Diagnosis of Actinomycosis is rarely considered. Gram and acid-fast stain are helpful in differentiating probable *Actinomyces* from aspirations and biopsies. Aspirations and biopsies (with or without CT or ultra sound guidance) are being used successfully to obtain clinical material for diagnosis, although sometimes surgery may be required. Isolation of the organism is extremely important to confirm the disease. For microbiologic identification, the avoidance of even a single dose of antibiotic is mandatory before isolation, which usually requires 5–7 days, but may take as long as 2–4 weeks. Sometimes a less fastidious co-pathogen, *Aggregatibacter actinomycetemcomitans* is a sole isolate and predicts the presence of *Actinomyces*.

TREATMENT

Actinomycosis requires prolonged treatment (6–12 months) with high dose of anti microbial agents. Usually cervicofacial infection responds to antibiotic alone but surgical drainage and excision may be required for large thoracic, abdominal and soft-tissue abscesses. *Actinomyces* are exquisitely susceptible to penicillin, extended-spectrum penicillin and wide range of β -lactam agents with or without combination of β -lactamase inhibiting agents. However, metronidazole is ineffective. Initially, aqueous penicillin G (2,50,000 U/kg/day) in four divided doses should be used intravenously for 2–6 weeks followed by 6–12 months of amoxicillin or oral penicillin. Latest evidences support an initial attempt at cure with medical therapy alone even in extensive disease. CT and MRI should be used to monitor the response to therapy. The prognosis is excellent with early diagnosis and surgical debridement and antimicrobial therapy. Treatment of periodontitis or caries may eliminate source of possible reinfection.

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IN A NUTSHELL

1. *Actinomyces israelii* is a filamentous, branching, gram-positive, catalase-negative and anaerobic bacillus.
2. It is a normal flora of mouth, GI tract and female genital tract; and attains access to tissue via mucosal breach, trauma or by aspiration.
3. Special hosts at risk are immunocompromised patients, AIDS and those with chronic granulomatous disease.
4. Actinomycosis is a chronic granulomatous, suppurative disease, characterized by extension to contiguous tissue with the formation of numerous draining fistulas and sinuses. Most common sites of infection are face, neck, abdomen and pelvis.
5. On Gram stain, *Actinomyces* cannot be distinguished from *Nocardia*.
6. Prolonged antimicrobial therapy with penicillin or cephalosporins is the key to treatment.

Chapter 29.21

Helicobacter pylori

John Matthai, Sarah Paul

Helicobacter pylori is a highly motile, slow-growing, Gram-negative spiral organism with the unique ability to produce large amounts of the urease enzyme. This enzyme is the key to colonization of the gastric mucosa. It is also the basis of rapid urease test (RUT) and the urea breath test which are indirect markers of the presence of the organism. *H. pylori* has a special affinity for the gastric mucosa and is etiologically linked to chronic active gastritis, peptic ulcer and gastric cancer in adults. However, this association is less well-established in children. In developing countries the infection is usually acquired in early childhood and persists throughout life unless a specific treatment is given. The chronic gastric inflammation which it induces, is asymptomatic in children, but may be a precursor for peptic ulcer disease and gastric malignancies in adulthood.

EPIDEMIOLOGY

Over the last two decades, the prevalence of *H. pylori* in the younger generation has declined in developed countries. However, the prevalence is still high in developing countries with lower socioeconomic status overcrowding and unhealthy living conditions. Studies in India show that more than 50% of children are infected by 10 years and 80% by 20 years of age.

H. pylori transmission is primarily by feco-oral route, but saliva and gastric secretions are also infective. Passively transferred immunity offers protection to infants.

Virulence factors help the organism establish itself in the adverse conditions of the stomach. They are of two types—colonization factors and factors responsible for tissue injury. The former include flagella, adherence factor and urease. The flagella help the organism move around in the stomach from areas of low pH to neutral pH to facilitate growth. Adherence factors help the organism to bind to specific receptor on the surface of the gastric epithelium. The organism does not invade the mucosa, but stays on the surface of the epithelium, under the mucus layer. The enzyme urease makes the surrounding environment alkaline by converting urea to ammonia. The factors that induce tissue injury include lipopolysaccharide, leukocyte recruitment and activating factors, vacuolating cytotoxin (VacA) and Cytotoxin-associated antigen (CagA). The first two not only stimulate the release of cytokines, but also have chemotactic properties to recruit and activate monocytes and neutrophils. VacA and CagA are strongly associated with toxin production and more severe inflammatory tissue injury.

DISEASE MANIFESTATIONS

Gastritis and Duodenal Ulcer

H. pylori is etiologically associated with chronic active gastritis, gastric ulcer and duodenal ulcer in children. However, only one in ten *H. pylori* infected persons develop peptic ulcer, while most infected individuals are asymptomatic.

Lymphoma and Adenocarcinoma

Primary gastric B-cell lymphoma, mucosal associated lymphoid type lymphoma (MALT lymphoma) and gastric adenocarcinoma have been reported in adults with chronic infection, but is infrequent in children.

Growth Retardation

The association with growth retardation is mainly from developed countries with little or no evidence from developing countries where the infection is wide spread.

Recurrent Abdominal Pain

Studies to associate recurrent abdominal pain (RAP) with *H. Pylori* over the years have given conflicting results. A recent meta-analysis of 38 studies concluded that there was no association between them. Guidelines from the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) support this view. Therefore, routine screening for *H. pylori* is not recommended in children with RAP at least in developing countries.

Iron Deficiency Anemia

There are conflicting reports on *H. pylori* being responsible for iron deficiency anemia (IDA). While studies from Greece, Korea and Turkey have demonstrated a causative effect, two recent studies concluded otherwise. Vendt et al., in a study on 363 children concluded that *H. pylori* seropositivity was not associated with anemia. Sarker et al., in a study from Bangladesh concluded that *H. pylori* was neither the cause of IDA nor a reason for treatment failure of iron supplementation in young children. The possible mechanisms for anemia in *H. pylori* infection include poor absorption of iron due to low gastric acid secretion and consumption of iron by the bacteria itself.

INVESTIGATIONS

Endoscopy-based tests are used for confirmation of *H. pylori* infection, while noninvasive tests are recommended for screening as well as for checking eradication or relapse.

Endoscopy-based Tests

Antral biopsy is required for diagnosis. The *gold standard* for the diagnosis is culture of the gastric mucosal biopsy. However, it is difficult and not routinely available. Rapid urease test (RUT) is easy to perform and has a specificity of around 98%, but the sensitivity is below 90%. This test is based on the unique ability of the organism to produce the enzyme urease which is indicated as a color change. Histology demonstrating *H. pylori* also has a specificity of 98%, but requires a trained pathologist and the sensitivity is below 90%. A combination of RUT and histology is accepted as a diagnostic alternative. Polymerase chain reaction (PCR) is emerging as a diagnostic test of the future.

Noninvasive Tests

Serology is unreliable in young children as the level of antibody produced is unpredictable. In addition, it cannot differentiate present from a past infection, since antibody persists for months after eradication. Both serum and saliva have been used in serology. ^{13}C urea breath test is difficult to perform in children below 5 years. Recently it has been shown that stool ELISA test for *H. pylori* antigen is a good noninvasive test to check eradication. The currently available second generation ELISA test which is based on monoclonal antibodies has a sensitivity and specificity of around 97%. The rapid fecal tests based on immunochromatography using monoclonal antibodies have a sensitivity of 88% and specificity of 93%.

Only those children whose abdominal symptoms are severe enough to suspect organic causes should be investigated. The primary goal is to determine the underlying cause of the symptoms

and not to confirm the presence of *H. pylori*. Therefore, endoscopy is the preferred method of investigation. Diagnostic testing is not recommended in children with functional abdominal pain. Endoscopy may also be selectively recommended for children with refractory iron-deficiency anemia and those whose first-degree relatives have gastric cancer.

TREATMENT

Guidelines from ESPGHAN and NASPGHAN, eradication of the organism is recommended only in children with *H. pylori*—positive peptic ulcer disease (PUD). In those who are positive for *H. pylori* but have no endoscopic lesions, the option of treatment may be offered after an informed discussion with the parents. Parents should be informed of the potential adverse effects of drugs and that eradication of *H. pylori* may not necessarily result in improvement of symptoms. Treatment must also be recommended for children with *H. pylori* infection whose first-degree relative have gastric cancer. Drugs used to treat *H. pylori* are given in **Table 1**.

Conventional first line treatment is twice daily triple drug regimen comprising one proton pump inhibitor (PPI) and two antibiotics (amoxicillin plus clarithromycin or metronidazole) for 10–14 days. Sequential therapy involves a PPI and amoxicillin for 5 days followed by 5 days of triple therapy (a PPI with clarithromycin and metronidazole/tinidazole). Sequential therapy is at least as effective as standard triple drug therapy in children and is considered a first line treatment option (**Table 2**).

Eradication of the organism should be confirmed even if children become asymptomatic after therapy. This should be done 4–8 weeks after completion of treatment with a noninvasive test like ^{13}C urea breath test or a monoclonal ELISA-based stool antigen test. A follow-up endoscopy is not routinely indicated unless the diagnosis is in doubt or if the patient remains symptomatic.

If first line therapy fails to eradicate the organism, repeat biopsy and culture/sensitivity testing is ideal. The treatment schedule may be modified either by adding an antibiotic or bismuth, using a different antibiotic or increasing the duration of therapy. Second line or salvage therapy as given below should be given for up to 14 days.

1. **Quadruple therapy:** PPI + metronidazole + amoxicillin + bismuth
2. **Triple therapy:** PPI + levofloxacin (moxifloxacin) + amoxicillin

Failure of therapy may be due to multiple factors, often acting simultaneously and include: primary antibiotic resistance to clarithromycin, levofloxacin and metronidazole; poor patient compliance; insufficient antibiotic concentration in the cardia of stomach resulting in the organism persisting there; presence of dormant coccoid forms of the bacteria, which are antibiotic resistant; and high bacterial load and presence of VacA and CagA.

Table 1 Drugs used in treatment of *H. pylori* infection in children

Drugs	Dose
Amoxicillin	50 mg/kg/day, max dose: 1 g twice daily
Clarithromycin	20 mg/kg/day, max dose: 500 mg twice daily
Metronidazole	20 mg/kg/day, max dose: 500 mg twice daily
Omeprazole (PPI)	1–2 mg/kg/day, max dose: 20 mg twice daily
Bismuth subsalicylate	< 10 years: 262 mg, > 10 years: 525 mg

Table 2 First line treatment options

A. Triple drug regimen:
1. Amoxicillin + clarithromycin + PPI (e.g., Omeprazole)
2. Amoxicillin + metronidazole + PPI (e.g., Omeprazole)
3. Bismuth subsalicylate + amoxicillin + metronidazole
B. Sequential therapy:
Omeprazole + amoxicillin for first 5 days
Followed by
Omeprazole + clarithromycin + metronidazole for 5 days

The sharp decline in eradication rate over the last decade, with standard regimens has been a major cause of worry. In spite of unraveling the *H. pylori* genome, efforts at vaccine development has stalled in the last decade. Designing a new therapeutic regimen containing a single antibiotic with lesser side-effects that ensures better patient compliance is the challenge for the future.

IN A NUTSHELL

1. Infection with *H. pylori* is common among children in developing countries, but most infected children are asymptomatic.
2. Transmission occurs primarily by feco-oral route and virulence factors decide the severity of infection and inflammation.
3. Chronic gastritis and duodenal ulcer are the only diseases in children with a proven association.
4. The association between *H. pylori* and recurrent abdominal pain is still unproven.
5. Endoscopic antral biopsy and rapid urease test, histology and culture are the preferred method of primary diagnosis.
6. Eradication status may be confirmed with noninvasive tests like ^{13}C urea breath test or monoclonal stool antigen test.
7. First line therapy includes the standard *triple drug regimen* or sequential therapy for 14 days.

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Chapter 29.22

Anaerobic Infections

Rekha Harish, Anuj Bhatti

Anaerobes do not multiply in oxygen and have variable susceptibility to oxygen. Most normal flora anaerobes are extremely oxygen sensitive, while those that cause infections are more aerotolerant. The aerotolerance of several anaerobes is through the production of superoxide dismutase, they produce on exposure to oxygen. The negative oxidation–reduction potential (Eh) of the environment is important for their survival.

The exact incidence is difficult to ascertain, as these require special methods to transport, cultivate, isolate and identify. Further, these infections are generally caused by indigenous local microflora invading due to the immunocompromised status of the host. In one of the largest prospective study, they accounted for 5.8% of all bacteremia episodes: 8.7% in the newborn period and 4.8% in children over 1 year of age. The species of anaerobes most frequently isolated from clinical infections in decreasing frequency are as follows:

- Gram-negative rods (*Bacteroides*, *Prevotella*, *Porphyromonas*, *Fusobacterium*, *Bilophila* and *Sutterella*),
- Gram-positive cocci (primarily *Peptostreptococcus*)
- Gram-positive spore-forming (*Clostridium*)
- Nonspore-forming bacilli (*Actinomyces*, *Propionibacterium*, *Eubacterium*, *Lactobacillus*, and *Bifidobacterium*)
- Gram-negative cocci (mainly *Veillonella*).

Important anaerobic infections are listed in **Table 1**. Anaerobes are frequently isolated in combination with other facultative or aerobic bacteria. **Table 2** enlists such exclusive, predominant pathogens in pediatric patients. Certain anaerobes have a predilection for specific anatomical sites. The major anaerobic pathogens in the upper and lower respiratory tract are *Peptostreptococcus* spp., pigmental *Prevotella* and *Porphyromonas*

spp., and *Fusobacterium* spp., *B. fragilis*, anaerobic Gram-positive cocci and *Clostridium* species are frequently isolated from intra-abdominal and female genital infections.

CLINICAL SPECTRUM

Bacteremia

Children with chronic debilitating disorders such as malignancy, immunodeficiency, or chronic renal insufficiency usually present with anaerobic bacteremia. Routine blood cultures are rarely positive for anaerobes in pediatric patients. The strain of anaerobic organisms isolated depends to a large extent on the portal of entry and the underlying disease. *Bacteroides* spp., including *B. fragilis* group, are the predominant isolates when the gastrointestinal tract is the probable portal of entry. The ear, sinus, and oropharynx predisposes to bacteremia by *Peptococcus* sp. and *Fusobacterium* spp.

Skin/Soft Tissue Infections

Common risk factors for the anaerobic infections of the skin and soft tissues are injury by foreign body, ischemia, malignancy, or surgery. The anatomic sites that are subject to fecal or oral contamination are particularly at risk. These include wounds associated with surgery of the intestine or pelvic tract, human bites, decubitus ulcers in the perineal area, pilonidal cysts, omphalitis, and cellulitis. These can present with putrid discharge, gas production, and extensive tissue necrosis with a tendency to burrow through subcutaneous and fascial planes. Infectious gangrene is a rapidly progressive infection that involves extensive necrosis of the subcutaneous tissues and overlying skin. It includes:

- Necrotizing fasciitis (Streptococcal gangrene)
- Gas gangrene (*Clostridium myonecrosis*) and anaerobic cellulitis
- Progressive bacterial synergistic gangrene
- Localized skin necrosis complicating cellulitis
- Gangrenous cellulitis in the immunocompromised patient.

Myonecrosis is a rapidly progressing fatal disease. It requires early and prompt management. The necrotic tissue often needs excision

Table 1 Common organism involved in anaerobic infections in children

Organism	Infectious site
Gram-positive cocci <i>Peptostreptococcus</i> spp. <i>Microaerophilic streptococci</i>	Respiratory tract, intra-abdominal and subcutaneous infections Sinusitis, brain abscesses
Gram-positive bacilli Nonspore-forming <i>Actinomyces</i> spp. <i>Propionibacterium acnes</i> <i>Bifidobacterium</i> spp.	Intracranial abscesses, chronic mastoiditis, aspiration pneumonia, head and neck infections Shunt infections (cardiac, intracranial) Chronic otitis media, cervical lymphadenitis
Spore-forming <i>Clostridium</i> spp. <i>C. perfringens</i> <i>C. septicum</i> <i>C. sordellii</i> <i>C. difficile</i> <i>C. botulinum</i> <i>C. tetani</i>	Wounds and abscesses, sepsis Sepsis Necrotizing infections Diarrheal disease, colitis Botulism Tetanus
Gram-negative bacilli <i>Bacteroides fragilis</i> group (<i>B. fragilis</i> , <i>B. thetaiotaomicron</i>) Pigmental <i>Prevotella</i> and <i>Porphyromonas</i> spp. <i>Prevotella oralis</i> <i>Prevotella B. oris-buccae</i> <i>P. bivia</i> , <i>P. disiens</i> <i>Fusobacterium</i> spp. <i>F. nucleatum</i> <i>F. necrophorum</i>	Intra-abdominal and female genital tract infections, sepsis, neonatal infection Orofacial infections, aspiration pneumonia, periodontitis Orofacial infections Orofacial infections, intra-abdominal infections Female genital tract infections Orofacial and respiratory tract infections, brain abscesses, bacteremia Aspiration pneumonia, bacteremia

Table 2 Infections in which anaerobes are exclusive, predominant or important

Intoxications Tetanus Wound botulism	Neonatal infections Scalp infections Neonatal pneumonia Omphalitis Bacteremia Conjunctivitis of newborn Infant botulism Necrotizing enterocolitis
Head and Neck Chronic and acute otitis media Chronic sinusitis Exudative tonsillitis Tonsillar or pharyngeal abscess Gingivitis Cervical lymphadenitis	Intra-abdominal Complication of appendicitis Peritonitis Pylephlebitis Liver abscess Ascending cholangitis Subphrenic abscess Abscess following visceral perforation Other intra-abdominal abscess Wound infection following abdominal surgery or trauma Complication of diverticulitis
Central nervous system Brain abscess Ventriculitis following neurological shunts Orogenic meningitis, extradural or subdural empyema	
Cardiovascular Bacteremia Endocarditis	
Pleuropulmonary Pneumonia secondary to obstructive process Aspiration pneumonia Lung abscess Bronchiectasis Thoracic empyema	Miscellaneous Breast abscess Gas gangrene (clostridial myonecrosis) Gas forming cellulitis Synergistic necrotizing cellulitis Necrotizing fasciitis Bacterial conjunctivitis

and debridement. Crystalline Penicillin in high-dose (250,000 U/kg/day divided every 4–6 hours IV) is recommended. Alternatively Clindamycin can also be given (25–40 mg/kg/day divided every 6–8 hours IV). Hyperbaric oxygen has been tried but its role in routine clinical settings is not yet proven. Even with early aggressive therapy the prognosis is poor and amputation of affected limbs may be required.

Central Nervous System Infections

Anaerobic organisms are frequently isolated from brain abscess. The spread to the central nervous system can occur from the infections in the contiguous sites like chronic mastoiditis, sinusitis, or otitis media. Seeding from the distant infections (e.g., in lung or abdomen) can occur through hematogenous route. The most common causative organisms are Gram-positive anaerobic cocci, *Bacteroides species* (including *Bacteroides fragilis*), fusobacterium, and actinomyces.

Upper Respiratory Tract/Infections

Chronic infections of the sinuses, ear, periodontal, peritonsillar, parapharyngeal and retropharyngeal areas are associated with anaerobes. Children with poor oral dental hygiene or drug induced hypertrophy of gums are predisposed to have anaerobic periodontal disease.

Vincent's angina (known as acute necrotizing ulcerative gingivitis or trench mouth). It is mixed anaerobic bacterial-spirochetal infection of the gingival margin and floor of the mouth. Children present with acute gingival pain, foul breath, and pseudomembrane formation.

Ludwig angina is a life-threatening infection which originates in the dental region and can rapidly result in airway obstruction caused by cellulitis of the sublingual and submandibular space.

Lemierre syndrome or postanginal sepsis, is a suppurative infection of the lateral pharyngeal space. It usually begins as Epstein Barr Virus or other infections of the pharynx. It later becomes complicated with anaerobic and other polymicrobial organisms which results in unilateral septic thrombophlebitis of the jugular venous system with septic pulmonary embolization. Clinical signs include trismus, unilateral painful neck swelling, and dysphagia with signs of sepsis and respiratory distress. *Fusobacterium necrophorum* is the most common anaerobe involved.

Lower Respiratory Infections

Anaerobes have been isolated from children with aspiration pneumonia, lung abscess, necrotizing pneumonia, and empyema. Normal oral flora is generally reflected in these pleuropulmonary infections. Fistula of the chest wall overlying the intrathoracic infections should provide the characteristic clinical clue. The infections are usually polymicrobial. The organisms include anaerobic gram-positive cocci, *Bacteroides sp.* (including *B. fragilis* and *B. melaninogenicus* groups), *Fusobacterium sp.*, and *Veillonella sp.* In unusual cases, particularly in patients with poor dental hygiene, aspirated oral contents may contain the anaerobe *Actinomyces israelii*, resulting in pulmonary actinomycosis.

Intra-abdominal Infections

Anaerobes outnumber aerobes (1,000:1) in the normal gastrointestinal tract; hence any defect in the intestinal wall/viscus as a result of infarction/obstruction/trauma, would result in the invasion of the peritoneal cavity with anaerobic organisms. Localized or generalized peritonitis will result in abdominal, retroperitoneal, and visceral abscesses, secondary to appendicitis, diverticulitis, necrotizing enterocolitis, pelvic inflammatory disease, and tubo-ovarian infection, surgery, or trauma. Anaerobes are isolated in at least half of cases of pyogenic liver abscess. A colonic source is usually the initial source of infection. The most prevalent anaerobes in liver abscess are anaerobic and microaerophilic streptococci (not true anaerobes), *Fusobacterium spp.*, *B. fragilis* group, and pigmented *Prevotella* and *Porphyromonas spp.*

Typhlitis describes neutropenic enterocolitis of ileo-cecal region which is often a mixed infection. Clinically it is characterized by abdominal pain, diarrhea, fever, and abdominal distention. The clinical course can be dramatic and outcome devastating.

Other Sites

Anaerobic infection in the vicinity of the bone can lead to contiguous infection. Occasionally, anaerobic osteomyelitis, particularly of fingers and toes, be seen in diabetes, neuropathies, vasculopathies, and coagulopathies because these conditions can produce hypoxic necrosis. Anaerobic infections of the heart (pericarditis), kidneys (renal and perirenal abscesses) and are rare. Enteritis necroticans (pigbel) is a rare but often fatal gastrointestinal infection that most commonly follows ingestion of a large meal in a previously starved child or adult.

Neonatal Infections

Anaerobic neonatal bacteremia is estimated to occur in 1.8 cases per 1,000 livebirths. Prolonged labor, premature rupture of membranes, amnionitis, prematurity, fetal distress, and respiratory difficulty are attributed maternal risk factors predisposing to bacteremia. Most often isolated organisms are *Bacteroides sp.*, *Clostridium sp.*, and *Fusobacterium nucleatum*. Anaerobes are also implicated in necrotizing enterocolitis. They have also been isolated from other neonatal infections viz. conjunctivitis, omphalitis and pneumonia. Neonatal tetanus is discussed elsewhere in the book.

Infantile Botulism

Infantile botulism is occasionally encountered in this part of the world due to common practice of giving honey as prelacteal feed to the newborn. It is caused by absorption of heat-labile neurotoxin produced by *Clostridium botulinum*. The toxin does exert its toxicity through affecting the transmission at all peripheral cholinergic junctions. It does not cross blood brain barrier but blocks the release of acetylcholine from the nerve terminal in response to depolarization. The main clinical feature of the syndrome is constipation (95%) and lower motor neuron symmetric, descending paralysis. Cranial nerve palsy is often the first clinical manifestation presenting with drooling, weak cry/suck or subdued facial expression as the common initial symptoms.

The time between the onset of constipation and onset of weakness ranges from 0 to 24 days (mean 11 days). Progression is more severe in infants especially less than two months. Autonomic dysfunction is quite common. Parasympathetic nervous system is more vulnerable to cholinergic blockade. The clinical manifestations may include decreased salivation, distension of abdomen and bladder, decreased bowel sounds, and fluctuations in blood pressure, heart rate, and skin color. Respiratory support may be required, though often in first week. Diagnosis is mainly on clinical grounds as stool samples for spores and toxins are often unavailable and culture takes up to 6 days for a positive yield. There is no role of antibiotics as they may increase the pool of toxin in bowel by causing bacterial lysis). Botulism Immune Globulin (BIG IV) a human derived antitoxin was conclusively demonstrated to be beneficial in a recent RCT in California.

Diagnosis is purely on clinical grounds. Respiratory support may be required in first week of illness. There is no role of antibiotics as they may increase the pool of toxin in bowel for absorption (toxin liberated after bacterial cell death).

DIAGNOSIS

High index of clinical suspicion is required to recognize the risk factors for anaerobic infections. Anaerobes form normal microflora at the skin and mucosal tissues, hence the swab samples from skin and mucosal surfaces and various secretions are not recommended. Aspirates of infected sites, abscess material, and biopsy specimens may reveal organisms. The samples must be transported immediately to the laboratory. The use of anaerobic transport medium is helpful. Gram staining of abscess fluid from suspected anaerobic infections is helpful even if the organisms do not grow in culture.

TREATMENT

The principles of managing anaerobic infections include

1. Neutralization of toxins
2. Prevention of local proliferation
3. Prevention of spread into healthy tissues.

Antitoxins can be used for the neutralization of toxin in tetanus and botulism. Debridement of necrotic tissue and draining of pus can prevent the local proliferation of anaerobes. Antibiotics can be used to avoid local proliferation and spread of infection. Penicillin still remains the preferred drug for the anaerobes of oral origin. β -lactamase production is the most common mechanisms of resistance to Penicillin by these organisms. In these scenario

metronidazole, penicillins combined with β -lactamase inhibitors (ampicillin-sulbactam, ticarcillin-clavulanate, and piperacillin-tazobactam), carbapenems (imipenem and meropenem), clindamycin, and cefoxitin are effective. Antibiotics for anaerobic infections should be given for prolonged periods because of their tendency to relapse (up to 3 weeks in serious infections). Role of hyperbaric oxygen in the treatment of anaerobic infections still remains uncertain.

PREVENTION

Prophylactic use of antibiotics against anaerobes is recommended in all elective intra-abdominal and oropharyngeal surgeries. Cefoxitin is the preferred drug for these conditions.

Superficial wounds suspected to be caused by anaerobes should be irrigated copiously and allowed to heal by secondary intention, especially if they are ragged lacerations caused by animal or human bites.

IN A NUTSHELL

1. Anaerobic infections are frequently caused by indigenous local microflora invading human body secondary to the immunocompromised status, breach in mucosa or presence of foreign body.
2. They should be clinically suspected in any foul-smelling lesion/discharge, black discoloration of exudate, *sulfur granules* in discharge, necrotic gangrenous tissue or evidence of free gas in tissue; cases of bacteremia/endocarditis without any growth on aerobic blood cultures.
3. Swab samples from skin and mucosal surfaces and various secretions are not recommended for diagnosing anaerobic infections. However, aspirates of infected sites, abscess material and biopsy specimens may reveal organisms.
4. Debridement of necrotic tissue and drainage of pus is a useful adjunct along with antibiotics to curtail local proliferation.
5. Rational Antibiotic stewardship in aerobic infections have been effective in reducing the rates of *C. difficile anaerobic* infection, an anaerobic infection which is currently a rising cause of health-care associated infections.

MORE ON THIS TOPIC

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Section 30 MYCOBACTERIAL INFECTIONS

Section Editor Soumya Swaminathan

Chapter 30.1

Antitubercular Drugs

Geetha Ramachandran

Mycobacterial infections represent some of the most difficult diseases to treat; because of the rich lipid content and a complex cell envelope, mycobacteria are refractory to most antimicrobial agents. In addition, mycobacteria are facultative intracellular parasites, capable of surviving and persisting within the host macrophage. Given this intracellular infestation, agents that are to be effective in controlling and/or killing the pathogen must also be able to penetrate the host cell that harbors the mycobacteria. Intracellular effectiveness is therefore an additional attribute necessary for adequate antimycobacterial therapy. The chronic nature of mycobacterial infections generally necessitates prolonged therapy over several months. An ideal agent should therefore have low toxicity and be effective at low dose levels. The slow growing nature of the microorganisms, adherence to treatment, adverse events and drug resistance pose therapeutic challenges.

DRUGS

Four groups of organisms can be found in patients infected with tuberculosis (TB)—(1) actively growing extracellular organisms, which are present in large numbers in aerated cavities (2) intermittent slowly growing organisms in the infected site (3) organisms surviving environmental conditions with low pH and (4) fully dormant organisms surviving in anaerobic conditions. The key actions of anti-TB drugs are:

- Bactericidal action, indicating their capacity to kill actively growing bacilli;
- Sterilizing action, indicating their ability to kill semi-dormant organisms;
- Preventing the emergence of resistance.

Anti-TB drugs differ in their ability to kill actively metabolizing extracellular population (bactericidal), their action on semi-dormant bacilli (sterilizing action) and in prevention of emergence of resistant strains. The different groups of drugs used to treat TB are shown in **Table 1**. *First-line* agents possess a high-degree

of efficacy with minimal toxicity and *second-line* agents having either less efficacy, greater toxicity or both. Patients infected with TB can be cured of the disease by treatment with first-line drugs. Occasionally, however, because of bacterial resistance or patient-related factors, it may be required to change to second-line drugs.

The modern short-course chemotherapy aims at rapid bactericidal and sterilizing action. Combination chemotherapy is employed because of the usual presence of spontaneously resistant mutants to one drug, which, with single drug therapy, may multiply and replace the killed microorganisms. Improper chemotherapy leads to acquired drug resistance. Children usually do not depict primary resistance unless the source case is suffering with resistant bacilli.

Isoniazid

Isoniazid (INH), hydrazide of isonicotinic acid was introduced in clinical practice in 1952. It is a first-line drug used to prevent and treat TB. It is quite cheap and well-tolerated. It is bactericidal to rapidly multiplying mycobacteria, and is bacteriostatic to slow growing mycobacteria. The minimal bacteriostatic concentration of INH is 0.025–0.05 µg/mL. It is remarkably selective for mycobacteria. *Mycobacterium kansasii* is the only nontuberculous mycobacteria that is susceptible to isoniazid. INH inhibits the synthesis of mycolic acid which is an essential mycobacterial cell wall component.

Metabolism

Isoniazid attains therapeutic concentrations in blood, cerebrospinal fluid (CSF) and caseous granulomas. It undergoes acetylation in the liver by N-acetyl transferase. There are two forms of the enzyme which bring about this reaction; fast metabolizers, who acetylate INH rapidly than others, the half-life being bimodal. The rate of acetylation is genetically determined. Thus, rapid acetylators metabolize INH faster than slow acetylators, the former having 4–5 times higher quantity of the enzyme than slow acetylators. Isoniazid acetylator status can be determined using phenotypic or genotypic methods. The distribution of rapid and slow acetylators of INH differs across different racial and ethnic populations. The frequency of the slow allele has been reported as 10% in people belonging to the mongoloid race such as Eskimos, Japanese, Chinese, 90% in Middle East, 60% in the Negroid, Caucasian and south Indians, and 72% in the USA.

Table 1 Groups of drugs used to treat tuberculosis

Group	Group name	Drugs
1	Oral first-line agents	Isoniazid (INH), rifampicin, ethambutol, pyrazinamide, rifabutin, rifapentine
2	Injectables	Kanamycin, amikacin, capreomycin, streptomycin
3	Fluoroquinolones	Moxifloxacin, levofloxacin, ofloxacin
4	Oral bacteriostatic second-line agents	Ethionamide, prothionamide, cycloserine, terizidone, para-amino salicylic acid
5	Others with unclear efficacy	Clofazimine, linezolid, amoxicillin-clavulanic acid, thiacezone, meropenem-clavulanic acid, imipenem/cilastatin, high-dose INH, clarithromycin

Adverse Events

Peripheral neuropathy and central nervous system (CNS) effects are common side-effects because of the use of INH due to pyridoxine (vitamin B₆) deficiency. The hepatotoxic side-effects due to INH have been reported to be caused by the N-acetyl hydrazine metabolite. Further, it has been demonstrated that slow acetylators are likely to be affected more than rapid acetylators.

Pharmacokinetics

Isoniazid is absorbed readily through oral or parenteral administration. Aluminum containing antacids could interfere in the absorption. Peak plasma concentrations of about 3–5 µg/mL are achieved at about 1–2 h. INH readily diffuses into all body fluids and cells. The drug can be detected in pleural fluid and ascitic fluid, and plasma and CSF concentrations are similar. INH penetrates into caseous material and is not bound to serum proteins; hence plasma and saliva concentrations are similar. About 75–95% of INH is excreted within 24 hours in the urine as metabolites.

Rifampicin

Rifampicin, also known as rifampin belongs to the rifamycin group, and came into use in 1967. It is bactericidal and inhibits growth of most Gram-positive and Gram-negative microorganisms. It is an important component of first-line treatment regimen of tuberculosis. It inhibits growth of *Mycobacterium tuberculosis* at concentrations of 0.005–0.2 µg/mL in vitro. It inhibits growth of certain nontuberculous mycobacteria such as, *M. kansasii*, *Mycobacterium avium*, *Mycobacterium intracellulare* and *Mycobacterium scrofulaceum*. Rifampicin, being red, imparts a red-orange color to body excretions, predominantly urine and sweat and tears to a lesser extent after intake. Serum drug concentrations are reduced when the drug is taken along with meal.

Mechanism of Action

Rifampicin acts by inhibiting ribonucleic acid (RNA) synthesis in the bacteria by blocking the bacterial DNA-dependent RNA polymerase, thereby suppressing initiation of chain formation. Rifampicin resistance develops quickly during treatment; as a result of mutations that modify rifampicin binding site on the polymerase, leading to reduced affinity for rifampicin. Resistant mutations have been mapped to the *rpoB* gene, which encodes the beta subunit of RNA polymerase.

Adverse Effects

Hepatotoxicity is the most important adverse effect and patients treated with this drug should get their liver function tested at frequent intervals. Further, in view of being an effective liver enzyme-inducer, rifampicin administration can also lead to other adverse reactions when used with other medications. The other common side-effects include fever, rashes, gastrointestinal disturbances and immunological reactions. Rifampicin is excreted in breastmilk.

Pharmacokinetics

Rifampicin is readily absorbed from the gastrointestinal tract; maximal concentrations of about 7 µg/mL are attained at 2–4 hours after intake of 600 mg per dose. Aminosalicic acid may delay the absorption reduce drug levels. Following absorption, rifampicin is eliminated through the bile by enterohepatic circulation. During this process, the drug gets deacetylated; the deacetylated product has full antibacterial activity. About 30% of the drug is excreted in urine. Rifampicin gets distributed in effective levels in many organs and body fluids, such as the CSF.

Pyrazinamide

Pyrazinamide, a synthetic pyrazine analog of nicotinamide is a first-line drug used to in the treatment of tuberculosis. It is bactericidal at a slightly acidic pH and kills organisms residing within monocytes at a drug concentration of about 12.5 µg/mL.

Mechanism of Action

Pyrazinamide is a prodrug which inhibits growth of *M. tuberculosis* by diffusing into the bacilli, where it gets converted to the active form, pyrazinoic acid by the enzyme, pyrazinamidase. Mutations in the *pncA* gene, which codes for pyrazinamidase, leads to pyrazinamide resistant *M. tuberculosis* strains. Certain pyrazinamidase resistant strains with mutations in the *rpsA* gene have also been reported. Pyrazinoic acid accumulation impairs membrane potential and interferes in energy production, essential for bacterial survival at the site of infection. Pyrazinoic acid inhibits translation by binding to ribosomal protein S1, which explains the ability of pyrazinamide to kill dormant mycobacteria.

Adverse Effects

The most common adverse event of pyrazinamide is joint pains (arthralgia); however, this is usually not very severe, requiring patients to stop taking this drug. Pyrazinamide can cause gout by reducing renal excretion of uric acid. Another serious adverse event is hepatotoxicity, which is dose-related. Other adverse effects include anorexia, nausea and vomiting, skin rash, sideroblastic anemia, pruritus, and urticaria.

Pharmacokinetics

Pyrazinamide is readily absorbed through the gastrointestinal tract and is distributed widely throughout the body. Serum concentrations of about 45 µg/mL are attained at 2 hours following oral administration of 1 g of pyrazinamide. The primary route of elimination is renal. Pyrazinamide undergoes hydroxylation to pyrazinoic acid and then to 5-hydroxy pyrazinoic acid, which is the main excretory product.

Ethambutol

Mechanism of Action

Ethambutol (EMB) is bacteriostatic and is also effective against *M. avium complex*, and *M. kansasii*. Ethambutol exerts its action by inhibiting cell wall formation. Mycolic acids get attached to 5'-hydroxyl groups of D-arabinose residues in arabinogalactan, forming mycolyl-arabinogalactan-peptidoglycan complex. It prevents synthesis of arabinogalactan by disrupting arabinosyl transferase.

Adverse Effects

The most important adverse event is optic neuritis, causing visual acuity and loss of ability to differentiate red and green, this being dose related and reversible. The drug enhances blood urate concentrations because of reduced renal excretion of uric acid.

Pharmacokinetics

About 75–80% of an orally administered dose is absorbed through the gastrointestinal tract. Plasma concentrations of about 5 µg/mL are attained at 2–4 hours following a single dose of 15 mg/kg. The half-life of ethambutol is 3–4 hours. About two-thirds of an ingested dose of ethambutol is excreted unchanged in the urine within 24 hours; about 15% is excreted as two metabolites, namely aldehyde and a dicarboxylic acid derivative. It is well distributed in fluids and body tissues.

Aminoglycosides

Streptomycin was the first antibiotic used to cure tuberculosis. It is bactericidal and can inhibit growth of *M. tuberculosis* at concentrations as low as 0.4 µg/mL. Amikacin, kanamycin and capreomycin have limited antitubercular activity in acid environments. Further, their limited ability to target intracellular organisms means that they have poor activity against *M. tuberculosis* residing within host macrophages, which may explain lack sterilizing activity in vivo. Thus, these antibiotics are part of second-line of treatment of tuberculosis.

Mechanism of Action

Aminoglycosides are protein synthesis inhibitors. They exert their action by binding to 16S rRNA of the 30S subunit of the bacterial ribosome, thereby interfering with binding of formyl-methionyl-tRNA to the 30S subunit. This causes codon misreading, inhibition of protein synthesis and finally bacterial cell death.

Adverse Effects

The common adverse events are nephrotoxicity, ototoxicity, vestibular toxicity and electrolyte abnormalities. The vestibular portion of cranial nerve VIII (the vestibulocochlear nerve) is affected, leading to tinnitus, ataxia and vertigo.

Pharmacokinetics

Aminoglycosides are absorbed completely after injection. They are known to cross poorly into CSF, but diffuse into bronchial secretions. About 99% of aminoglycosides get excreted in the urine as the parent drug. Aminoglycosides are minimally protein bound and highly water-soluble, explaining their limited ability to cross lipid-containing membranes. The aminoglycosides show concentration dependent killing; 1 g intramuscular dose produces peak plasma concentrations of 25–30 µg/mL.

Ethionamide

Mechanism of Action

Ethionamide is a second-line drug used to treat drug-resistant tuberculosis. Drug concentrations of about 0.6–2.5 µg/mL can suppress multiplication of *M. tuberculosis*. It is a prodrug, which gets activated by a monooxygenase, namely ethA, present in *M. tuberculosis*; this binds to NAD⁺ causing inhibition of InhA.

Adverse Effects

The most common adverse events are anorexia, vomiting and nausea and can cause a metallic taste. Ethionamide shares structural similarity with methimazole, and has been reported to inhibit thyroid hormone synthesis. This could lead to hypothyroidism.

Pharmacokinetics

Oral administration of 1 g of ethionamide produces maximal plasma concentrations of about 20 µg/mL at 3 hours. Its half-life is about 2 hours. Ethionamide is widely distributed; concentrations in blood and various organs are similar. Significant levels are present in CSF. Only about 1% of ethionamide is excreted unchanged in the urine.

Para-aminosalicylic Acid

Although para-aminosalicylic acid (PAS) is less potent compared to INH, rifampicin, ethambutol, pyrazinamide, and streptomycin, it is still useful to treat multidrug-resistant tuberculosis. PAS is a prodrug and gets incorporated into the folate pathway to generate a hydroxyl dihydrofolate antimetabolite, which in turn blocks dihydrofolate reductase (DHFR) enzymatic activity.

Side Effects

Nausea, vomiting, and diarrhea are common; the delayed-release formulation can overcome this problem. It can cause drug-induced hepatitis. Patients with glucose-6-phosphate dehydrogenase deficiency should not be prescribed aminosalicylic acid, since it can cause hemolysis. Goiter can also be encountered, due to inhibition of synthesis of thyroid hormones by aminosalicylic acid. Phenytoin levels are likely to increase because of drug interactions. Rifampicin coadministration leads to reduction in rifampicin concentrations by 50%.

Pharmacokinetics

Para-aminosalicylic acid is rapidly absorbed from the gastrointestinal tract. A single oral dose of 4 g of the free acid leads to peak plasma concentrations of about 75 µg/mL at 1.5–2 hours. The drug gets distributed throughout the total body water and attains high concentrations in pleural fluid and caseous tissue. The drug has a short half-life of 1 hour, and plasma concentrations become negligible within 4–5 hours. About 50% of the drug is excreted in urine, more than 50% as acetylated metabolite. Excretion of PAS is impaired during renal dysfunction and is not recommended in such patients.

Cycloserine

Cycloserine is an antibiotic and a second-line drug used to treat drug-resistant tuberculosis. It is capable of penetrating into the CNS. Cycloserine exerts its action by inhibiting bacterial cell-wall biosynthesis. Cycloserine, at large doses increase the risk of occurrence of seizures and is contraindicated in persons with a history of epilepsy. It is readily absorbed following an oral dose. Maximal plasma concentrations are attained at about 3–4 hours and are in the range of 20–35 µg/mL. It is distributed throughout tissues and body fluids. Concentrations in CSF and plasma are similar. Toxic concentrations may accumulate in patients with impaired renal function.

Fluoroquinolones

The potency of fluoroquinolones against *M. tuberculosis* is as follows: moxifloxacin above levofloxacin above ofloxacin, with levofloxacin having at least twice the activity of ofloxacin. Of note, the activity of levofloxacin and ofloxacin against bacterial pathogens are decreased 4–16 fold at an acidic pH of 5.0. These drugs have also shown in vitro activity against intracellular bacteria. Fluoroquinolones are well-tolerated, common adverse events being gastrointestinal disturbances, CNS manifestations, prolongation of QT interval and arthropathy. These are readily absorbed following oral administration, with bioavailability of 85–95% for ofloxacin, more than 99% for levofloxacin and 86–91% for moxifloxacin. Absorption is substantially reduced by coadministration of multivalent cations. Food can delay absorption and lower peak concentrations. The fluoroquinolones have good penetration into body fluids, including CSF.

Linezolid

Linezolid has demonstrated consistent in vitro activity against *M. tuberculosis*. It has shown intracellular activity against *M. tuberculosis*, and its activity in a murine model being less than that of rifampicin but greater than that of INH. Linezolid has bactericidal activity against drug-susceptible strains in the exponential growth phase, but against nonreplicating *M. tuberculosis* in a latent growth phase, only the highest concentrations showed any bactericidal activity, suggesting limited sterilizing ability. Adverse events associated with its use are GI disturbances, hematologic toxicity, and neurotoxicity. Linezolid is rapidly absorbed with an oral

Table 2 Doses of first-line anti-TB medications for children

Drug	Daily dosage (mg/kg)	Intermittent dosage (mg/kg)	Therapeutic range (µg/mL)	Route of elimination
INH	10	15	3–6	Renal
Rifampicin	15	15	8–24	Biliary
Pyrazinamide	35	35	20–50	Renal
Ethambutol	15	30	2–6	Renal
Streptomycin	15	30	35–45	Renal

Table 3 Dosages of second-line anti-TB drugs for children and therapeutic range

Drug	Dose recommended (mg/kg)	Maximum dose	Therapeutic range (µg/mL)
Kanamycin	15–30 once daily	1 g	35–45
Amikacin	15–22.5 once daily	1 g	35–45
Capreomycin	15–30 once daily	1 g	35–45
Ofloxacin	15–20 once daily	800 mg	8–12
Levofloxacin	7.5–10 once daily (twice daily for < 5 years)	750 mg	8–12
Moxifloxacin	7.5–10 once daily	400 mg	3–5
Ethionamide	15–20 once daily	1 g	1–5
Cycloserine	10–20 once or twice daily	1 g	20–35
PAS	150 daily in 2–3 divided doses	12 g	20–60
Linezolid	10 twice daily (once daily for > 10 years)		Not known

bioavailability of 100%. A high-fat meal may delay absorption and reduce peak concentration. Linezolid has good tissue penetration, including lung and epithelial lining fluid.

Tables 2 and 3 summarize the dosages of first and second-line anti-TB agents for use in children.

NEW DRUGS

TMC 207

TMC 207 belongs to a new chemical family and targets adenosine triphosphate (ATP) synthase, causing inadequate synthesis of ATP. It has a minimum inhibitory concentration (MIC) of 0.06 µg/mL against *M. tuberculosis* and does not have any cross resistance with existing anti-TB drugs. The activity of TMC 207 is time-dependent and depends on the duration of the active concentration of the drug remaining greater than the MIC. At concentrations 10 times and 100 times the MIC, the drug was observed to be highly bactericidal against *M. tuberculosis*, which was observed after 6 days of incubation. The effectiveness and safety of TMC 207 have not been studied adequately in children. According to the Centers for Disease Control and Prevention (CDC), TMC 207 may be used on a case-by-case basis in children when an effective treatment regimen cannot be otherwise provided.

Nitroimidazopyrans

Nitroimidazo-oxazine PA-824

PA-824 is currently among the more promising new drugs used to treat tuberculosis. It is a derivative of metronidazole. PA824 has potent anti-TB activity, with MIC of 0.125 µg/mL against drug-susceptible and resistant strains of *M. tuberculosis*. It is bactericidal against both replicating and nonreplicating bacilli. It inhibits synthesis of ketomycolates, which is an essential component of the mycobacterial cell wall.

OPC-67683 (Delamanid)

OPC-67683, a nitro-dihydro-imidazooxazole, is a derivative of metronidazole. Its drug action is similar to that of PA 824 and MIC against *M. tuberculosis* ranges is about 10 times lower than the MIC of PA824. It also has potent activity against intracellular *M. tuberculosis*. However, its bioavailability is 10 times less than PA824. Clinical trials in children using delamanid are in progress in South Africa.

SQ109

SQ109 is an analog of ethambutol. It has a MIC of 0.5 µg/mL for *M. tuberculosis* and does not have cross resistance with ethambutol. It targets the formation of cell wall by inhibition of trehalose monophosphate transferase. It possesses anti-TB activity when used singly and also when combined with other drugs.

Benzothiazinones and Dinitrobenzamides

Drug susceptible and MDR TB are uniformly susceptible to these drugs. These compounds target enzymes required for synthesis of arabinans, which are essential parts of the cell wall.

IN A NUTSHELL

1. Intracellular effectiveness is an additional attribute necessary for adequate antimycobacterial therapy.
2. The chronic nature of mycobacterial infections generally necessitates prolonged therapy over several months.
3. An ideal agent should have low toxicity and be effective at low-dose levels. The slow growing nature of the microorganisms, adherence to treatment, adverse events and drug resistance pose therapeutic challenges.
4. First-line drugs include INH, Rifampicin, Pyrazinamide, Ethambutol, and Streptomycin.
5. Important second-line drugs include ethionamide, cycloserine, other aminoglycosides, fluoroquinolones, PAS and linezolid.

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Chapter 30.2

Tuberculosis

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Tuberculosis (TB) is a major cause of disease, both pulmonary and extrapulmonary and death in young children in India, reflecting the high disease burden in adults. Major risk factors include poverty with associated undernutrition, overcrowding and human immunodeficiency virus (HIV) infection. This chapter reviews the disease burden and the natural history of disease in children with TB and describes the current status of diagnosis, treatment and prevention of TB in children.

DISEASE BURDEN

Most cases of TB in children occur in the TB-endemic countries but the actual burden of childhood TB is unknown. In 2012, WHO estimated that globally there were 530,000 TB cases among children (under 15 years of age), and 74,000 TB deaths (among HIV negative children), 6% and 8% of the global totals, respectively. India has one of the highest TB burdens globally, accounting for 25% of the 8.6 million new TB cases annually. While the burden of childhood TB in India is not known, regional data from the World Health Organization (WHO) indicate that sputum microscopy smear-positive TB in children (< 14 years old) accounts for 0.6–3.6% of all reported cases.

In 2013, 85,000 children were diagnosed and treated in the Revised National TB Control Program (RNTCP), accounting for ~7% of total TB cases in the public sector in India. This proportion has been fairly stable over the past few years. However, because the majority of children are sputum microscopy smear negative, these figures underestimate the true burden of childhood TB. It is estimated that childhood TB constitutes 10–20% of all TB in high-burden countries, accounting for 8–20% of TB-related deaths. Further, many young children with extrapulmonary and more severe forms of TB are probably treated in the private sector and data regarding these cases is not available in the public domain. A recent modeling paper suggests that India accounts for 27% (22–33) of the total burden of pediatric TB in the high burden 22 countries.

A nationwide survey in India among young children showed very high figures of annual risk of *Mycobacterium tuberculosis* infection in almost all the regions—highest in north zone (1.9%) followed by west zone (1.8%), east zone (1.3%) and lowest in the south zone (1.1%). HIV infection increases susceptibility to infection with *M. tuberculosis*, the risk of progression from infection to TB disease as well as reactivation of latent TB. Increasing levels of co-infection with TB and HIV in children have been reported from countries with dual epidemics, with prevalence of HIV in TB-infected children ranging from 10% to 60%. Management of both infections poses a challenge to clinicians.

Children serve as a *sentinel*, reflecting ongoing TB transmission in the community, and drug resistance in this group mirrors the situation in the adult population in the region. The occurrence of drug-resistant TB (DR-TB) among children has been documented by several groups. In the Western Cape, repeat surveys among children, done in 1997–1998, 2001–2002 and again in 2005–2006, showed that resistance to isoniazid (INH) or rifampin (RIF) increased from 6.9% to 12.9% to 15.1% and multidrug resistance from 2.3% to 5.6% to 6.7% respectively. Drug resistance among children

has been documented in both pulmonary and extrapulmonary disease. The Global TB Report 2013, reviewing data from many countries reporting drug resistance survey and surveillance data, concluded that *drug resistance is as likely among children as among adults*. In India, the few reports available indicate that DR-TB does occur in children, with the rate reflecting the DR-TB rates in adults in that geographic region. **Table 1** summarizes key differences between adults and children with TB.

Human immunodeficiency virus co-infection has had a major impact on the epidemiology of TB, especially in sub-Saharan Africa. In addition to an increase in the absolute number of TB patients, HIV induced a pronounced shift in the age and gender profile of TB patients with more young adults and women of child-bearing age being affected. This has resulted in increased TB exposure of young and vulnerable children living in HIV-affected households, as shown by high rates of TB exposure within the first 6 months of life in babies born to HIV-infected mothers, and high disease rates among HIV-infected infants in South Africa.

In India, because HIV prevalence in the population as well as among pregnant women is low (approximately 0.3%), the epidemiology of TB has not been affected much. However, at the individual level, in HIV-affected households, both adults and children are at higher risk of TB. Regular screening for TB, early diagnosis and treatment of active disease and preventive therapy should be implemented widely in order to reduce the burden of TB among HIV-infected individuals.

NATURAL HISTORY OF DISEASE

Figure 1 shows the schematic timeline following primary pulmonary infection with *M. tuberculosis*. Pulmonary infection occurs when a few bacilli reaches a terminal airway and establish infection. A localized inflammatory process occurs within the lung, referred to as the primary (Ghon) focus, from where bacilli drain via lymphatics to the regional lymph nodes. Before acquired immune responses are able to control and localize the infection, bacilli enter the systemic circulation via the regional lymph nodes with occult hematogenous spread. Bacilli can survive in various organs for prolonged periods depending on local conditions and pathogen-host interactions.

Age is an important variable, and the youngest of all children have the most rapid disease progression. The clinical syndromes associated with primary *M. tuberculosis* infection in children are summarized in the following phases:

- **Phase 1** occurs 3–8 weeks after primary infection and usually presents with fever, a visible primary complex on chest radiograph (CXR) and hypersensitivity manifestations such as erythema nodosum and tuberculin skin test (TST) conversion. This stage may be relatively asymptomatic and is often missed.
- **Phase 2** occurs 1–3 months after primary infection and follows hematogenous spread. This represents the period of highest risk for the development of tuberculous meningitis (TBM) and disseminated (miliary) TB in young children, though these can occur at any time.
- **Phase 3** occurs 3–7 months after primary infection and manifests as intrathoracic lymph node enlargement in young children (< 5 years of age) and reactive pleural effusions in older children.
- **Phase 4** lasts for 1–3 years after primary infection. It represents the period of osteoarticular TB in children under 5 years of age and adult-type disease in adolescents. The risk of disease progression is least between 5 years and 10 years of age.
- **Phase 5** more than 3 years after primary infection. By this time the highest risk period has passed, although delayed onset adult-type TB may present in adolescents.

Table 1 Differences between adult and childhood tuberculosis

Aspect	Adults	Children
Epidemiology	Relatively well-quantified burden—2.1 million new cases each year in India, of which ~1.5 million in RNTCP	Poorly quantified global and country disease burden—~85,000 cases/year in RNTCP
Pathogenesis	Usually <i>adult-type</i> lung disease	Usually intrathoracic lymph node disease, but extra-pulmonary disease common
Transmission	Lung cavitary disease highly infectious	Paucibacillary disease; epidemiologic marker of transmission
Drug resistance	Acquired drug resistance more common	Usually primary (transmitted) drug resistance
Exposure history	May not be contributory	Essential part of diagnostic work-up
Risk of progression to disease	Relatively low risk of progression to disease following TB exposure/infection unless immunocompromised	Greatest risk of progression in the very young and/or immunocompromised
Preventive therapy	Not recommended, except in immunocompromised adults	Definite value in young (< 5 years of age) contacts and all immunocompromised children
Imaging	Chest radiographs (CXR) required, only if sputum negative for AFB	CXR (with both anteroposterior and lateral views, of good quality, and properly read) is important investigation
Microbiological studies	Sputum smear microscopy for AFB first test. Xpert MTB/Rif recommended in sputum smear negative, HIV+, retreatment and other patients at high risk for MDR-TB	Gastric aspirate or induced sputum must be collected (young children cannot expectorate); Xpert MTB/Rif has better yield than smear
Treatment (drug-susceptible TB)	With four drugs in intensive phase.	With three or four drugs depending on likelihood of isoniazid resistance and HIV co-infection
Pharmacokinetics	Acetylator status influences isoniazid levels	Younger age and stunting also lower blood levels of anti-TB drugs. Faster metabolism in young children alters PK
Prognosis	Good outcomes with timely and appropriate treatment	Excellent outcomes achievable; long-term sequelae common with delayed diagnosis, especially tuberculosis meningitis

Abbreviations: RNTCP, Revised National TB Control Program; TB, tuberculosis; MDR-TB, multidrug resistance tuberculosis; PK, pharmacokinetics; AFB, acid-fast bacillus; CXR, chest radiographs.

Source: Adapted from Perez-Velez CM, Marais BJ. Tuberculosis in children. *N Engl J Med*. 2012;367:348-61.

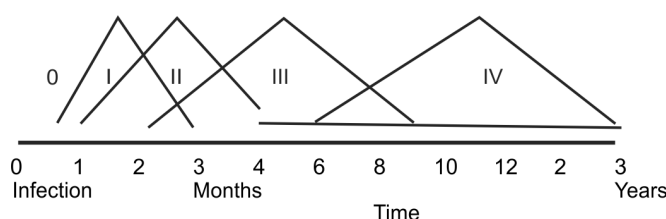


Figure 1 Schematic timeline following primary pulmonary infection with *M. tuberculosis*

Adapted timeline of tuberculosis:

- 0 Incubation
- I Tuberculin skin test conversion
- II Ghon focus and/or disseminated (miliary) disease
- III Lymph node disease (< 5 years of age)/pleural effusion (> 5 years of age)
- IV Adult-type disease (> 10 years of age)

DISEASE SPECTRUM

Intrathoracic Disease

Pulmonary involvement in children presents with a diverse spectrum of pathology that can be visualized on CXR. However, CXR is not a very sensitive tool and many parenchymal and lymph node lesions can be missed. Taking anteroposterior (AP) as well as lateral views and using a standardized disease classification system is important for management as well as for reporting.

Primary (Ghon) focus The primary focus is usually single, though there may be multiple foci, which are variable in size and which may show an overlying pleural reaction. Local complications

include parenchymal destruction with cavity formation, as well as intrabronchial spread with bronchopneumonic consolidation (**Figs 2 and 3**).

Lymph node disease Involvement of the intrathoracic lymph nodes (perihilar and/or paratracheal) (**Figs 4 and 5**) is considered the radiological hallmark of primary infection. Lymph nodes can rupture into airways, or compress them from outside; such complications are most common in young children because of smaller airways. Airway compression results when the trachea or main bronchus is surrounded by diseased lymph nodes; best visualized on an overpenetrated CXR. Various disease presentations include partial airway obstruction with a check-valve effect and alveolar hyperinflation, or total airway obstruction with alveolar collapse. Caseating pneumonia often causes an expansile pneumonic process with visible parenchymal breakdown. Rare complications include diaphragmatic palsy, broncho- or tracheoesophageal fistula, and a unilateral chylothorax.

Pleural or pericardial effusion Effusions represent a hypersensitivity response to TB antigens (**Fig. 6**). Isolated pleural effusions are unusual in children more than 3 years of age and tend to develop within a few months after primary infection. TB empyema occurs when bacteria multiply within a loculated fluid collection. Pleural effusion can be diagnosed on CXR and ultrasound and confirmed by examining aspirated fluid (high protein and lactate dehydrogenase, lymphocytic pleocytosis). Pericardial effusion usually develops when a subcarinal lymph node erupts into the pericardial space. Ultrasound is the most sensitive test to confirm a pericardial effusion; constrictive pericarditis can develop later.

Disseminated disease Though dissemination is common following primary infection, it rarely progresses to disseminated disease

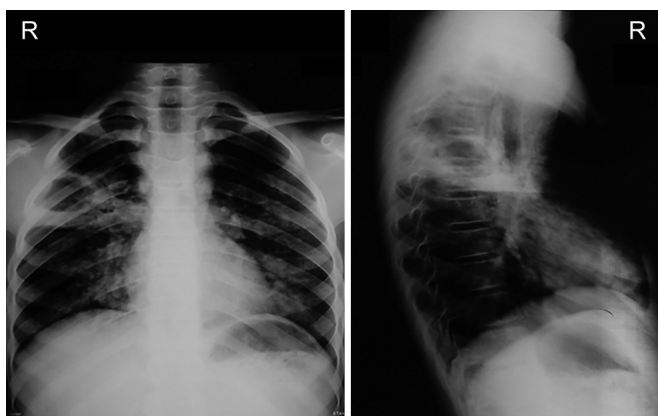


Figure 2 Parenchymal destruction with cavity formation

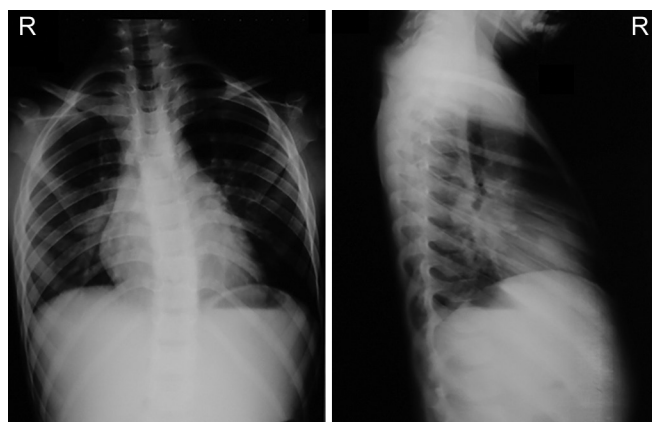


Figure 4 Perihilar lymph nodes



Figure 3 Intrabronchial spread with bronchopneumonic consolidation

except in very young (<2-3 years of age) and immunocompromised children. CXR is usually diagnostic of miliary disease with even-sized miliary lesions (<2 mm) distributed bilaterally into the very periphery of the lung. In HIV-infected children, the differential diagnosis includes lymphocytic interstitial pneumonitis (LIP) and opportunistic infections such as *Pneumocystis jiroveci* pneumonia (PCP), which have a similar radiological picture. The presence of parotid enlargement, clubbing and generalized superficial lymphadenopathy is more suggestive of LIP, while children with PCP are dyspneic and sick. A trial of antibiotics may have to be given to distinguish between these conditions.

Adult-type disease Adult-type disease is common during adolescence, but can occur from 8 years onward. Similar to adults, the apical and posterior segments of the upper lobes and the apical segment of the lower lobes are most commonly affected. Complications include progressive cavity formation and endobronchial spread.

Extrathoracic Disease

Cervical lymphadenitis The most common extrathoracic manifestation of TB in children is cervical lymphadenitis. The cervical mass is usually painless and includes matted nodes with surrounding inflammation, resulting in a cold abscess when the caseous material liquefies. The overlying skin gets discolored and spontaneous drainage and sinus formation may follow. Usually, a single group of lymph nodes is involved and generalized lymphadenopathy goes against the diagnosis of TB.

In an endemic country, a lymph node mass more than 2 cm in a child that persists despite a course of broad spectrum antibiotics has a high likelihood of TB. Establishing a definitive diagnosis is



Figure 5 Paratracheal and perihilar lymph nodes

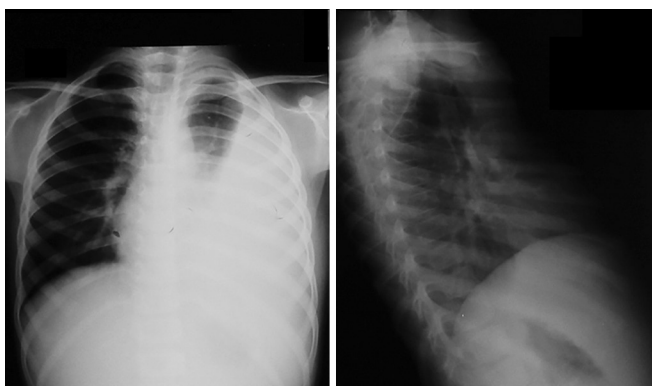


Figure 6 Tubercular pleural effusion (left)

preferable and can be done in a minimally invasive fashion using fine needle aspiration cytology (FNAC). The sensitivity of FNAC varies from 50% to 70% and a smear for acid-fast bacillus (AFB) staining must be done in addition to cytopathology to improve diagnostic sensitivity. If inconclusive, an open biopsy must be planned.

Tuberculous meningitis (TBM) (Also See Chapter 42.16) It is the most severe manifestation of childhood TB. Bacille Calmette-Guerin (BCG) vaccination provides some degree of protection (50-70%) against the severe forms of TB (miliary disease and TBM), but despite universal BCG vaccination in most TB endemic areas

severe disease manifestations still occur. TBM is most common in young children who frequently present with nonspecific symptoms—early diagnosis requires a high index of suspicion and is essential to ensure an optimal outcome. Symptoms of early disease include fever, listlessness, apathy, anorexia and/or failure to thrive and headache (in older children). As the disease progresses, convulsions and altered sensorium with or without neck stiffness and localizing neurological signs develop. The symptoms are due to the combined effects of raised intracranial pressure and cerebral vasculitis with brain ischemia/infarction. On CT or MRI scans, dense basal exudates and enlarged ventricles are the main findings.

Perinatal TB Newborn babies may acquire TB either congenitally or from their environment, and are at high risk of rapid disease progression. Congenital TB infection is acquired via the placenta or during birth by aspiration of infected amniotic fluid in which case primary lung involvement usually follows. This usually occurs when the mother develops TB during pregnancy, with hematogenous dissemination. Alternatively, the baby may inhale the bacillus after delivery (postnatal TB) if in close contact with an infectious adult.

Abdominal tuberculosis See Chapter 35.19.

DIAGNOSIS

The difficulty in confirming the diagnosis (needing multiple specimens other than sputum and a laboratory capable of performing culture), is due to the higher proportion of smear and culture-negative and extrapulmonary TB in young children, and the reluctance to collect specimens due to lack of training and/or awareness among healthcare workers.

The diagnosis of TB in children can be made on clinical and radiological grounds in the majority of cases, when bacteriological confirmation is not possible. Depending on the age of the child, site of disease, and available facilities, attempts can be made to obtain sputum, gastric aspirates, induced sputum, pleural or peritoneal fluid, CSF, nasopharyngeal aspirates, lymph node aspiration biopsy, or tissue biopsy and microbiologic confirmation increases with the number of samples. Invasive methods, such as bronchoalveolar lavage, bronchoscopic biopsy, or open lung biopsy may sometimes be required.

Children may be evaluated for TB when they fall sick and present for care (passive case finding), or as a result of contact investigation (active case finding).

Clinical Approach

A careful history including possible TB exposure in the wider family circle is important. Common symptoms include failure to thrive (deviation on growth chart) and reduced playfulness; low-grade persistent fever is less common. With airway involvement, the usual presenting symptom is a persistent nonremitting cough, unresponsive to antibiotics. There are many scoring systems available but none has been adequately validated; sensitivity and specificity is particularly poor in HIV-infected children. Diagnosis is based on a combination of clinical, radiological, and/or laboratory findings consistent with TB, together with epidemiological evidence of TB exposure or immunological evidence of *M. tuberculosis* infection [TST or interferon-gamma release assays (IGRAs)].

Imaging

Chest radiography is the most commonly performed and useful investigation. Both AP and lateral views should be taken; lateral views assist assessment of the mediastinum and hilar areas. However, pediatric radiographs must be interpreted properly as

hilar vasculature is often mistaken for lymph node enlargement. Ultrasound is useful to confirm pericardial or pleural effusions and abdominal lymphadenopathy, solid organ involvement or ascites. High-resolution computed tomography (CT) is very sensitive, but its use should be reserved for complicated intrathoracic cases due to high radiation exposure and cost. CT and MRI are useful for neurological involvement: MRI is more sensitive for detecting brainstem lesions or early perfusion defects in patients with TBM, and also provides better evaluation of the spine and soft tissues.

Laboratory Studies

Table 2 summarizes available diagnostic investigations. Sputum smear-microscopy is still the most widely available test, but has poor sensitivity in young children with paucibacillary disease who are unable to expectorate. The Xpert-MTB/RIF[®] assay is rapid and highly specific and using two sputum samples, it detects three times more cases than microscopy, and sensitivity is about 70% compared to culture. Immunological assays, the traditional TST and newer IGRAs fail to differentiate *M. tuberculosis* infection from TB disease. WHO recommends that IGRAs should not replace the TST for the detection of *M. tuberculosis* infection in low- or middle-income countries, although they provide similar information.

Expectorated sputum can be collected in children over 7–8 years of age, in younger children, gastric aspirates or lavage and induced sputa are preferred. **Table 3** provides an overview of specimen collection technique. The string test seems promising, although administration is difficult in young children who are unable to swallow the string containing capsule. Recently, stool has been suggested as a promising specimen for diagnosis in young children, but needs proper decontamination and adequate DNA extraction protocols. FNAC is very useful in children with a peripheral lymph node mass. The Union developed a pragmatic desk guide for TB diagnosis and management in resource-limited settings.

MANAGEMENT

Treatment of TB follows the basic principles of short-course therapy with a combination of bactericidal and sterilizing drugs and is similar to treatment of TB in adults. WHO recommends that children with uncomplicated disease, from settings with a low prevalence of INH resistance, can be treated with three drugs [INH, RIF and pyrazinamide (PZA)] during the 2-month intensive phase, followed by INH and RIF during the 4-month continuation phase. However, children with extensive and/or cavitary lung disease (implying a high organism load), or from settings with a high prevalence of INH resistance, should receive a fourth drug (ethambutol, which is safe in children of all ages within the recommended dosage range) during the 2-month intensive phase. Further, children with HIV infection or those living in an HIV prevalent region should receive four drugs. **Table 4** summarizes the mechanism of action, main adverse effects and recommended pediatric dosages of first-line TB drugs.

Drug resistance should be considered in children following documented contact with a patient with DR-TB, someone who died while on TB treatment without known drug susceptibility test results, is poorly adherent to therapy, or is a retreatment case. While data is limited, studies have shown that rates of drug resistance in children are generally similar to those in the adult population in the region.

All TB medications should preferably be given as directly observed therapy (DOT)—this can be by a health worker or parent. Proper counseling should be given to ensure compliance. In general, response to treatment is excellent with cure rates exceeding 90% in most settings. However, radiographic abnormalities especially hilar/mediastinal lymphadenopathy can persist and may take

Table 2 Summary of investigations to diagnose tuberculosis in children

Investigation	Uses	Strengths and limitations
Microbiological studies		
Microscopy	Diagnosis of TB	<i>Strengths:</i> Specificity high. Useful in all specimen types. Rapid (< 1 hour) detection. Low cost. <i>Limitations:</i> Sensitivity very low, especially in young children. Technician-dependent. Labor intensive. Unable to distinguish viable and dead bacilli
Culture	Diagnosis of TB; drug susceptibility testing	<i>Strengths:</i> Specificity high. <i>Limitations:</i> Sensitivity moderate to low in young children; slow turnaround time, need proper laboratory facilities
DNA detection (PCR) and CB-NAAT (Xpert MTB/Rif)		<i>Strengths:</i> Specificity high; Fully automated; Rapid turnaround. <i>Limitations:</i> Sensitivity moderate to low in young children; unable to distinguish viable from dead bacilli
Histopathological studies		
Stained tissue samples and fine needle aspiration cytology	Diagnosis of TB	Allows exclusion of other diagnoses (such as malignancy)
Immune-based studies		
TST; IGRA (e.g., Quantiferon Gold®)	Diagnosis of <i>M. tuberculosis</i> infection	Neither test can differentiate <i>M. tuberculosis</i> infection from TB disease; careful evaluation of discordant results <i>TST:</i> Requires a second visit after 48–72 hours, sensitivity lower in young and malnourished children <i>IGRAs:</i> Unaffected by BCG vaccination; single visit; reduced sensitivity in very young and/or immunocompromised children; collecting adequate volume of blood and indeterminate results problematic
Imaging		
Radiography CT and MRI Ultrasonography	Diagnosis of TB	Chest radiography (AP and lateral views) most common and useful; CT or MRI useful in uncertain or complicated cases and in CNS or bone and joint involvement; US useful to identify intra-abdominal/retroperitoneal lymphadenopathy or pleural/pericardial effusions, highly technician dependent

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; US, ultrasound; CNS, central nervous system; BCG, Bacille Calmette-Guerin; TST, tuberculin skin test; IGRA, interferon-gamma release assays.

Source: Adapted from Perez-Velez CM, Marais BJ. Tuberculosis in children. N Engl J Med. 2012; 367: 348–61.

Table 3 Specimens for microbiologic investigations

Specimen collection method	Problems/Benefits	Potential clinical application
Sputum	Not feasible in very young children; assistance and supervision may improve the quality of the specimen	Routine sample to be collected in children > 7 years of age (all children who can produce a good quality specimen)
Induced sputum	Comparable yield to gastric aspirate; no age restriction; specialized technique, which requires nebulization and suction facilities; potential transmission risk	To be considered in the hospital setting on an in- or outpatient basis
Gastric aspirate	Unpleasant procedure, but not difficult to perform; requires fasting, can be done as outpatient procedure; sample collection advised on at least 2 consecutive days	Routine sample collected in young children who cannot produce a good quality sputum specimen
Nasopharyngeal aspiration	Less invasive than gastric aspirate; no fasting required; comparable yield to gastric aspirate	To be considered in primary health care clinics or on an outpatient basis.
String test	Less invasive than gastric aspirate; tolerated well in children > 4 years; bacteriologic yield, feasibility and ideal string/capsule need further investigation	Useful in children who can swallow the capsule, but cannot produce a good quality sputum specimen
Bronchoalveolar lavage	Extremely invasive	Only for use in patients who are intubated or who require diagnostic bronchoscopy
Stool	Culture not practical, high contamination rates, DNA extraction difficult, <i>M. tuberculosis</i> excretion well documented	Reasonable yield using Gene Xpert in young children
Urine	Not invasive; excretion of <i>M. tuberculosis</i> components, including transrenal DNA	Lipoarabinomannan assay has poor sensitivity; unreliable in children
Blood/Bone marrow	Good sample sources to consider in the case of probable disseminated TB	Useful for the confirmation of probable disseminated TB in hospitalized patients
Cerebrospinal fluid	Fairly invasive; bacteriologic yield low, Gene Xpert useful	To be considered if signs of tuberculosis meningitis
Fine needle aspiration biopsy (FNAB)	Minimally invasive using a fine 23 G needle; excellent bacteriologic yield including Gene Xpert, minimal side-effects	Procedure of choice in children with superficial lymphadenopathy

Source: Adapted from Marais BJ, Pai M. Specimen collection methods in the diagnosis of childhood tuberculosis. Indian J Med Microbiol. 2006;24:249–51.

Table 4 Summary of first-line TB drugs and dosage recommendations in children

First-line drugs	Mode and mechanism of action	Main toxicities ¹	Daily dose mg/kg (range); [maximum dose] ²
Isoniazid (INH)	<i>Bactericidal</i> <ul style="list-style-type: none"> • Inhibits cell wall synthesis • Most potent early bactericidal activity offering the best protection to companion drugs • Contributes mainly by rapidly killing actively metabolizing extracellular bacilli, contributes to sterilization if given for a prolonged period 	Hepatitis; peripheral neuropathy	10 (7–15) [300 mg]
Rifampin (RIF)	<i>Bactericidal and sterilizing</i> <ul style="list-style-type: none"> • Inhibits RNA synthesis • Contributes by killing extracellular and slower growing intracellular bacilli, important contribution to sterilization 	Hepatitis; orange discoloration of secretions; drug-drug interactions	15 (10–20) [600 mg]
Pyrazinamide (PZA)	<i>Sterilizing</i> <ul style="list-style-type: none"> • Disrupts energy metabolism • Contributes by specifically killing bacilli that persist within the acidic centers of caseating granulomas. 	Hepatitis; arthralgia	35 (30–40) [2,000 mg]
Ethambutol (EMB)	<i>Bacteriostatic</i> <ul style="list-style-type: none"> • Inhibits cell wall synthesis • Contributes mainly by offering some additional protection against drug-resistant mutants 	Visual disturbance (acuity, color vision)	20 (15–25) [1,200 mg]
Suggested treatment regimens			
Disease category	Treatment regimen	Rationale	
Uncomplicated intrathoracic disease	INH, RIF, PZA (2-month intensive phase) INH, RIF (4-month continuation phase)	Organism load low, drug penetration good	
Extensive lung infiltrates and/or cavities, HIV co-infection, high baseline isoniazid resistance in community	Add EMB during 2-month intensive phase	Organism load high, drug penetration good, pre-existing drug resistance rates high	
Tuberculous meningitis (TBM) ³	Add fourth drug—at least during 2-month intensive phase. Prolong continuation phase to 10 months (WHO recommendation) Add steroids for 1 month	Organism load low, drug penetration variable, risk of severe immunomediated sequelae	
Severe airway compression	3 or 4 drug regimen depending on extent of lung infiltration/cavities Consider adding steroids for 1 month	Organism and drug penetration variable, ⁴ inflammation may worsen airway compression	
Recent exposure/infection	Preventive therapy	Organism load very low, drug penetration good	
No active disease	INH (6–9 months) INH, RIF (3 months)		

¹Hypersensitivity reactions and drug rashes may occur with any drug; ²WHO dosage recommendations for children; ³Recommendations around fourth drug and duration of therapy vary; ⁴Drug penetration into large cold abscesses may be limited, requiring surgical drainage

Source: Adapted from Perez-Velez CM, Marais BJ. Tuberculosis in children. *N Engl J Med*. 2012;367:348–61.

years to regress. **Flow charts 1A and B** shows the RNTCP algorithm for the diagnosis of TB in children. Poor clinical response to adherent treatment requires critical re-evaluation of the diagnosis, including other infections, immune reconstitution inflammatory syndrome (IRIS) and drug resistance. Good treatment outcomes can be achieved even in children with DR-TB if diagnosed on time and managed appropriately. In children with disseminated disease or TB affecting the CNS or bones and joints, treatment should be extended up to 12 months.

In HIV-infected children, immune recovery following ART initiation may unmask existing subclinical disease or induce paradoxical deterioration despite adequate TB treatment. The IRIS does not indicate treatment failure and treatment should usually not be interrupted; severe cases may require a course of corticosteroids. In order to reduce mortality due to TB, ART is best initiated within 8 weeks of starting TB treatment, and within 2–4 weeks in the severely immunocompromised. The only

exception for stopping or delaying ART would be patients with central nervous system TB, where IRIS can be dangerous. With HIV-associated TB, treatment should be daily.

DRUG-RESISTANT TUBERCULOSIS

Resistance to anti-tuberculosis (anti-TB) drugs is caused by spontaneous chromosomal mutations, present in low numbers in mycobacterial populations. An anti-TB drug suppresses replication of susceptible bacilli but allows DR mutants to replicate. Selection pressure imposed by an anti-TB drug on a population of *M. tuberculosis* results in a decline of drug-susceptible bacilli and advantageous reproduction of DR mutants, which is known as the *fall and rise phenomenon*. Consequently, DR mutants may outnumber drug-susceptible bacilli and become the dominant bacilli. This is acquired resistance, implying that resistance emerges during anti-TB treatment. An inappropriate drug regimen, use

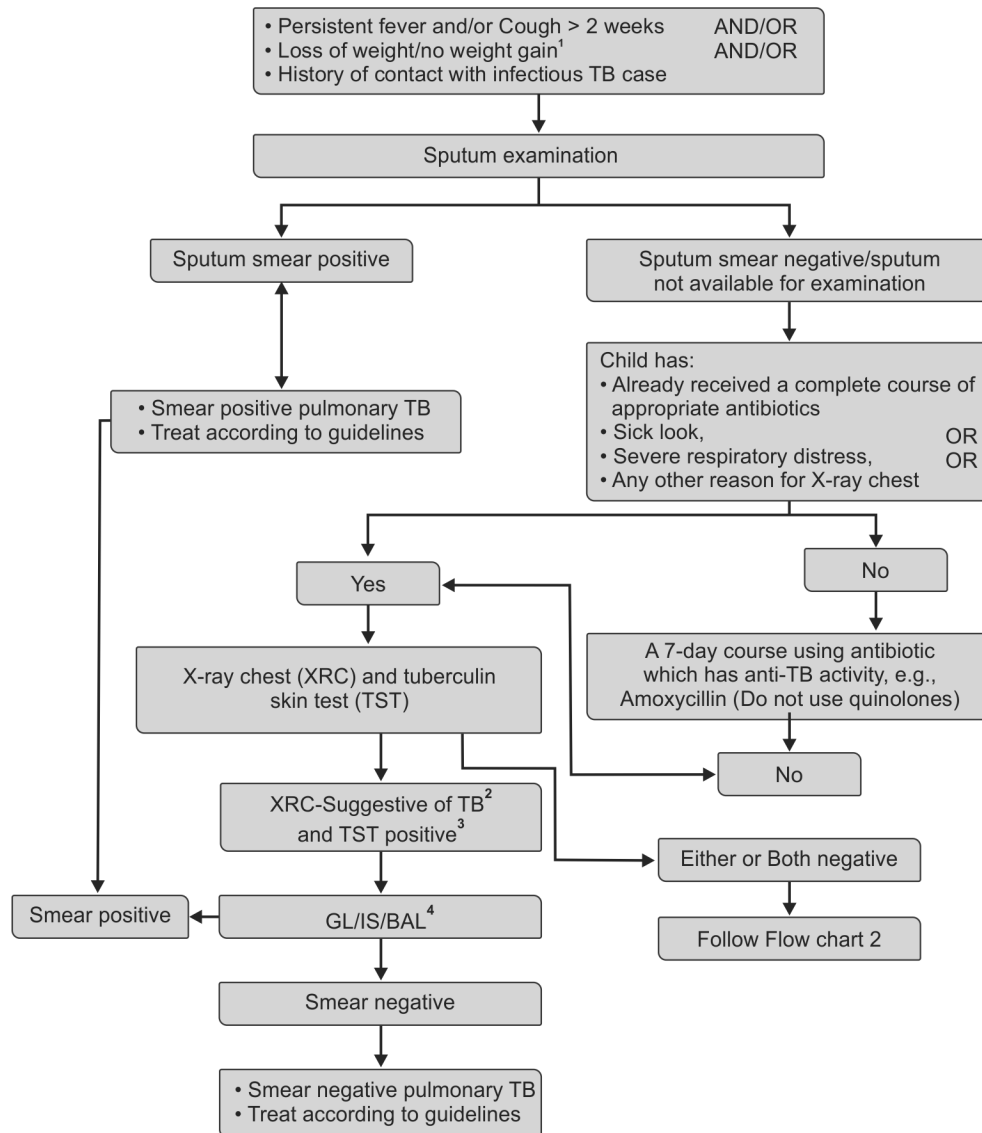
of a lower-than-recommended dosage, inferior drug quality and poor adherence to treatment are commonly associated with the emergence of drug resistance in individual patients.

Primary resistance in TB refers to patients infected with *M. tuberculosis* that is resistant to anti-TB drugs from the outset, prior to anti-TB treatment. DR-TB in children is usually due to transmission of resistant strains from an infected source (primary). Mono drug resistance is defined as resistance to one anti-TB drug, while poly drug resistance refers to resistance to two or more drugs. *Multidrug resistance* tuberculosis (MDR-TB) is a specific form of poly drug resistance defined as resistance to at least H and R.

Extensively drug-resistant TB (XDR-TB) is a special form of MDR-TB defined as resistance to at least H and R with further resistance to a fluoroquinolone and a second-line injectable agent (amikacin, kanamycin or capreomycin). The molecular basis of resistance to INH and RIF (and some other drugs) is now understood (**Table 5**).

The prevalence of drug-resistant TB in children has not been well-documented, but in general, the rates reflect the adult prevalence in that region. A recent modeling exercise estimated that around 999 792 (95% CI 937 877–1 055 414) children developed TB disease in 2010, of whom 31 948 (25 594–38 663) had multidrug-resistant disease. In India, MDR-TB in children has been found in

Flow chart 1A RNTCP diagnostic algorithm for pediatric tuberculosis



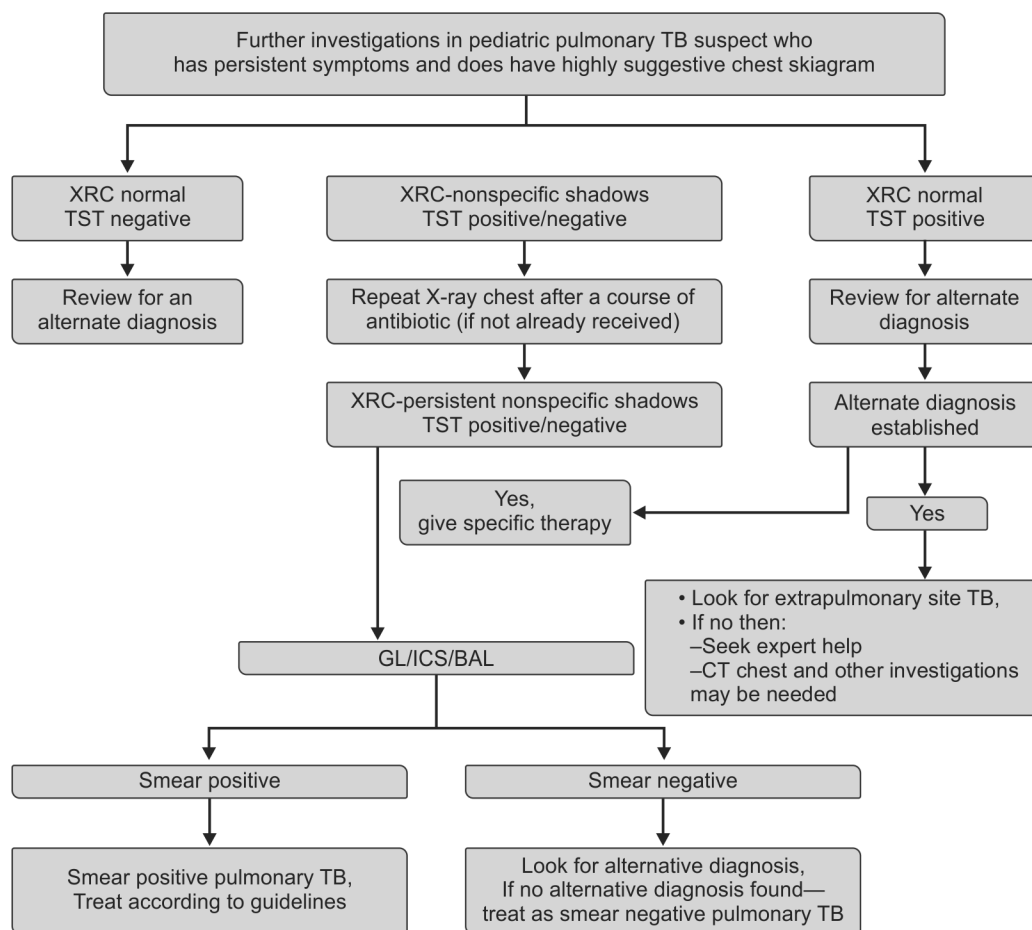
¹History of unexplained weight loss or no weight gain in past 3 months; loss of weight defined as loss of more than 5% body weight as compared to highest weight recorded in last 3 months

²Radiological changes highly suggestive of TB are Hilar/paratracheal lymphadenitis with or without parenchymal lesion, miliary TB fibrocavitary pneumonia

³If the radiological picture is highly suggestive of TB, then proceed to do further investigations irrespective of the TST result as the sensitivity of the test is not 100%

⁴All efforts including gastric lavage (GL)/induced sputum (IS) or bronchoalveolar lavage (BAL) should be made to look for acid-fast bacilli (AFB) depending upon the facilities

All efforts including gastric lavage (GL)/induced sputum (IS) or bronchoalveolar lavage (BAL) should be made to look for acid-fast bacilli (AFB) or for M to rapid culture or Gene Xpert[®] wherever facilities are available

Flow chart 1B RNTCP diagnostic algorithm for pediatric TB

Abbreviations: TB, tuberculosis; XRC, X-ray chest; TST, tuberculin skin test.

National Guidelines on diagnosis and treatment of Pediatric Tuberculosis, Accessed from: http://tbcindia.nic.in/Paediatric%20guidelines_New.pdf, accessed on August 20, 2014.

Table 5 Genetic sites for drug resistance in tuberculosis

Drug	Target	Gene
Isoniazid	Catalase-peroxidase enzyme	Kat G
Isoniazid-ethionamide	Mycolic acid synthesis	Inh A
Rifampin	RNA polymerase	Rpo B
Streptomycin	Ribosomal S12 protein 16S rRNA	Rpsl rrs
Quinolones	DNA gyrase	gyrA
Pyrazinamide	Pyrazinamidase-nicotinamidase	pncA
Ethambutol	Arabinosyl transferase	embcAB
PAS	Thymidylate synthase thy A	ThyA
Kanamycin	Ribosomal RNA	rrs

Abbreviations: PAS, para-aminosalicylate sodium.

Source: Adapted from Ormerod LP. Multidrug-resistant tuberculosis (MDR-TB): epidemiology, prevention and treatment. Br Med Bull. 2005;73-74(1):17-24.

3.5% in Chennai and 5% in Mumbai among all children with culture confirmed disease. A history of contact with an adult with MDR-TB is a critical pointer. Since only a small proportion of TB in children is culture-confirmed, drug resistance should be suspected whenever the child has been in contact with an adult with confirmed MDR-

TB or one who died or defaulted while on treatment, as well as a child who is failing or deteriorating on treatment. A diagnosis of *probable MDR-TB* can be made and the child started on treatment.

The principles of treatment regimen design for children are the same as for adults with MDR-TB. One major difference for children is that their treatment is often empiric and based on the drug susceptibility pattern of the source case, if available, or on past history of treatment. Depending on country guidelines, the regimen used is either individually constructed or a standardized one, such as the category IV regimen recommended by WHO.

The basic principles are the following:

- Use any first-line medication to which susceptibility is documented or likely (high-dose INH could be included routinely, unless high-level INH resistance or Kat-G mutation is documented).
- Use of at least four second-line drugs to which the strain is likely to be sensitive; one of these agents should be an injectable, one should be a fluoroquinolone, and PZA should be continued.
- All doses should be given using DOT to ensure that patients adhere to treatment.
- Treatment duration should be for 18–24 months, at least 12 months after the last positive culture/smear with minimal disease or 18 months with extensive (lung cavities or wide-spread parenchymal involvement) disease.

Table 6 shows the five groups of drugs placed by WHO used to treat DR-TB in children.

PREVENTION

Transmission within healthcare facilities is a possibility, especially when dealing with immunocompromised children and good ventilation is important in inpatient and outpatient facilities. Although BCG vaccination reduces the risk of disseminated (miliary) disease and TBM in young children, it offers no consistent protection against TB beyond the first few years of life. In HIV-infected children, BCG vaccination is contraindicated due to the risk of disseminated BCG disease. However, it is still given soon after birth in India, as population prevalence of HIV is very low and the benefits outweigh the risks. The development of a safe and effective vaccine remains a top global health research priority.

Isoniazid preventive therapy (IPT) for 6–9 months has been shown to provide excellent protection against TB disease, and has

been recommended by WHO for many years. Contact screening of family members living with an infectious patient and IPT for children under 6 years is a policy of RNTCP, but implementation is poor. Parents need proper counseling and advice in order to comply with giving drugs to an otherwise well child. Alternate regimens include INH and RIF for 3 months, which provides equivalent efficacy and improved adherence compared to 9 months of INH. A regimen of 12 doses of weekly rifapentine and INH was efficacious in adults, and is being studied in children.

All RIF and rifapentine-containing regimens interact with protease inhibitor-containing ART; this is less with rifabutin, but its use in preventive therapy regimens has not been evaluated. For children exposed to MDR-TB, there is no preventive therapy regimen that has been tested in clinical trials and the best option may be to keep such children under close observation. A regimen containing high dose INH, levofloxacin and ethambutol has been tried in South Africa to prevent MDR-TB in child contacts, but is not routinely recommended.

Table 6 Drugs used to treat TB in children

Group and Group name	Drugs	Dosage* (mg/kg)	Adverse events
1. First-line oral agents	Isoniazid	10–15	Hepatitis, peripheral neuropathy
	Rifampin	10–20	Hepatitis, discoloration of secretions
	Ethambutol	15–25 (DR-TB: 20–25)	Optic neuritis
	Pyrazinamide	30–40	Hepatitis, arthritis
2. Injectable agents	Kanamycin	15–30	Ototoxicity, nephrotoxicity
	Amikacin	15–22.5	As above
	Capreomycin	15–30	As above
	Streptomycin	15–20	As above
3. Fluoroquinolones	Ofloxacin	15–20	Sleep disturbance, gastrointestinal disturbance, arthritis, peripheral neuropathy
	Ciprofloxacin	20 twice daily	As above
	Levofloxacin	7.5–10 ⁺	As above
	Moxifloxacin	7.5–10	As above but including prolonged QT syndrome
4. Oral bacteriostatic second-line agents	Ethionamide	15–20	Gastrointestinal disturbance, metallic taste, hypothyroidism
	Prothionamide	15–20	As above
	Cycloserine	15–20	Neurological and psychological effects
	Terizidone	15–20	As above
	Para-aminosalicylic acid	150	Gastrointestinal intolerance, hypothyroidism, hepatitis
5. Agents with unclear efficacy	Clofazimine	3–5	Skin discoloration, xerosis, abdominal pain
	Linezolid	10 ⁺	Diarrhea, headache, nausea, myelosuppression, neurotoxicity, lactic acidosis, pancreatitis, and optic neuropathy
	Amoxicillin-clavulanic acid	10–15 (amoxicillin component) three times a day	Gastrointestinal intolerance, hypersensitivity reaction, seizures, liver and renal dysfunction
	Imipenem/cilastatin		As above
	Thiacetazone	2.5	Stevens Johnson syndrome in HIV-infected patients, gastrointestinal intolerance, hepatitis, skin reactions
	High dose isoniazid	15–20	Hepatitis, peripheral neuropathy, neurological and psychological effects
	Clarithromycin	7.5–15 twice daily	Gastrointestinal intolerance, rash hepatitis, prolonged QT syndrome, ventricular arrhythmias

Abbreviation: HIV, human immunodeficiency virus.

* Daily unless otherwise specified; + The stated doses is advised to be given twice a day for children less than 5 years

Source: Adapted from Seddon JA, et al. Caring for Children with Drug-Resistant Tuberculosis. American Journal of Respiratory and Critical Care Medicine. 2012;186(10):953–64.

MORE ON THIS TOPIC

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IN A NUTSHELL

1. The majority of children are sputum microscopy smear and culture negative, and hence the true burden of childhood TB is not known.
2. Human immunodeficiency virus infection increases susceptibility to infection with *Mycobacterium tuberculosis*, the risk of progression from infection to TB disease as well as reactivation of latent TB.
3. The youngest of all children have the most rapid disease progression and severe types of disease. Adult-type disease is common during adolescence, but can occur from 8 years onward.
4. The most common extrathoracic manifestation of TB in children is cervical lymphadenitis.
5. Bacteriologic confirmation of diagnosis needs multiple specimens other than sputum (gastric aspirate or induced sputum) and a laboratory capable of performing culture.
6. Diagnosis is based on a combination of clinical, radiological, and/or laboratory findings consistent with TB, together with epidemiological evidence of TB exposure or immunological evidence of *M. tuberculosis* infection (TST, interferon gamma release assays).
7. The Xpert-MTB/RIF[®] assay is rapid and highly specific and using two sputum samples, it detects three times more cases than microscopy, and sensitivity is about 70% compared to culture.
8. Treatment of TB follows the basic principles of short-course therapy with a combination of bactericidal and sterilizing drugs and is similar to treatment of TB in adults (6 months standard duration).
9. Drug resistance should be considered in children following documented contact with a patient with drug-resistant TB, someone who died while on TB treatment without known drug susceptibility test results, is poorly adherent to therapy, or is a re-treatment case.
10. Multidrug-resistant tuberculosis is treated with a 24-month regimen with second line drugs. Good treatment outcomes can be achieved even in children with DR-TB if diagnosed on time and managed appropriately.

Chapter 30.3

Atypical Mycobacterial Infections

C Padmapriyadarsini, Soumya Swaminathan

Atypical mycobacteria are also called nontuberculosis mycobacteria (NTM) or mycobacteria other than tuberculosis (MOTT). These are widely distributed in our environment. They have been isolated from soil, dust, biofilms and water—both natural as well as drinking water; the species, however, may differ from one geographical area to another. Exposure to these reservoirs is thought to be the source of human infection, though the specific source of infection cannot be usually identified.

CLASSIFICATION

Nontuberculosis mycobacteria are broadly divided into two main groups: Slow growers and rapid growers, according to their rate of growth on subculture. Currently, there are more than 140 identified NTM species and many of these have been reported to cause disease in both immunocompetent and immunocompromised individuals (Table 1).

EPIDEMIOLOGY

Studies across the world have reported an increase in the incidence or prevalence of NTM infection. The increase in the rate of NTM infection was usually associated with a decline in the rate of tuberculosis. The reasons for the increase in incidence and prevalence of NTMs include increased awareness of the disease as well as improved diagnostic techniques.

In India, till recently, culture was not a routine part of the diagnostic algorithm for tuberculosis (TB) and hence it is difficult to predict the exact magnitude of NTM in our country. Moreover, *M. tuberculosis* is much more common as a pathogen than NTM. Studies from various parts of the country have reported an NTM prevalence varying from 1–28% among chest symptomatics. With emergence of human immunodeficiency disease, a few studies have shown the presence of NTM in HIV infected patients in India.

Table 1 Classification of nontuberculosis mycobacteria

Slowly growing NTM	Rapidly growing NTM
Photochromogens—	<i>M. abscessus</i>
<i>M. kansasii</i>	<i>M. holsaticum</i>
<i>M. marinum</i>	<i>M. bollettii</i>
<i>M. simiae</i>	<i>M. chelonae</i>
Scotochromogens—	<i>M. fortuitum</i>
<i>M. avium</i>	<i>M. goodii</i>
<i>M. gordonae</i>	<i>M. massiliense</i>
<i>M. scrofulaceum</i>	<i>M. mucogenicum</i>
Nonchromogens—	<i>M. smegmatis</i>
<i>M. avium intracellulare</i>	<i>M. septicum</i>
<i>M. malmoense</i>	
<i>M. terrae</i>	
<i>M. ulcerans</i>	
<i>M. xenopi</i>	

PATHOGENESIS

Macrophages that phagocytose mycobacteria produce interleukin-12 (IL-12), which in turn, up regulates interferon-gamma (IFN- γ) production by lymphocytes. IFN- γ , in turn activates neutrophils and macrophages to kill the intracellular mycobacteria. This cycle between IFN- γ and IL-12 is critical for the control of mycobacterial infections. Specific mutations in the different genes responsible for synthesis of IFN- γ and IL-12 or in their receptors have been associated with disseminated NTM disease. Further, mutation in genes associated with synthesis of transducer and activator of transcription 1 (STAT1) have also been involved with NTM infection.

In children with human immunodeficiency virus infection, NTM disease occurs when the CD4 T lymphocytes have declined to less than 50 cells/mm³. Similarly, other conditions where cell-mediated immunity is depressed (e.g., long-term steroid treatment, anticancer chemotherapy, etc.) also predispose to NTM infection. An association has also been found between bronchiectasis, nodular pulmonary NTM infections and a particular body habitus (e.g., pectus excavatum, scoliosis, mitral valve prolapse). These phenotypic characteristic may represent markers for specific genotypes that affect both body morphology and NTM infection susceptibility.

Transmission

There is no evidence of animal-to-animal or human-to-human transmission of NTM. Human disease is presumably acquired from environmental exposure, though a specific source may be difficult to identify. The various species also vary greatly in their ability to cause disease. Portal of entry of NTM among children is not known, but predominance of cervical lymphadenitis suggests the oral route. It may be related to eruption of primary teeth, exposure to environmental mycobacteria in playing grounds, etc. Recently, a few cases of NTM wound infections have been described, especially after laparoscopic surgery.

CLINICAL PRESENTATION

Nontuberculosis mycobacteria cause four main types of diseases: (1) lymphadenitis, (2) chronic pulmonary, (3) postinoculation and (4) disseminated disease.

Lymphadenitis

This is the most common form of NTM disease in children. Occurring insidiously, most frequently in children between 1 year and 5 years of age, cervical lymph nodes are most commonly affected. Submandibular, submaxillary or preauricular lymph nodes may also be involved besides cervical lymphadenitis. The involved lymph nodes are generally unilateral, nontender and unresponsive to conventional antibiotics. Nodes may enlarge rapidly and even rupture to form sinus or fistula resulting in prolonged local drainage. Spontaneous regression can occur. Other lymph node groups like mediastinal lymph nodes may also be involved.

Superficial lymphadenitis, especially cervical lymphadenitis, in children is caused mostly by *M. avium* complex, *M. scrofulaceum* or *M. malmoense* though *M. tuberculosis* is still a more common cause of lymphadenitis in TB-endemic countries. In a clinical trial of TB lymphadenitis in children, Jawahar et al. found *M. tuberculosis* in more than 99% of patients. Unlike TB lymphadenitis, with NTM lymphadenitis there is typically no history of exposure to TB, screening tuberculin skin tests of the child and family members are usually negative and chest radiograph is normal.

No risk factors predisposing to NTM cervical lymphadenitis in children have been identified, but children with Bacille Calmette-Guerin (BCG) immunization have a reduced risk of NTM cervical lymphadenitis.

Chronic Pulmonary Disease

This is the most common form of NTM disease in adults—middle-aged men are more frequently affected. Patients present with chronic or recurrent productive cough, fatigue, malaise, dyspnea, fever, chest pain, hemoptysis and weight loss. Auscultation may reveal crepitations and wheeze in the lung fields. Predisposing factors for this form of NTM disease usually includes local lung lesions like old tubercular cavities, chronic obstructive pulmonary disease (COPD), bronchiectasis, and cystic fibrosis.

Postinoculation

This form of NTM disease can occur following injections as post-injection abscesses, following laparoscopic surgeries at the port site (surgical inoculation), keratitis, through cuts and abrasions, during water games like swimming or attending to fish tanks, etc. Post injection abscesses usually develop due to use of contaminated multidose vaccines, 1–12 months after vaccination and tend to be localized. Buruli ulcer caused by *M. ulcerans* can present as single firm painless subcutaneous nodule on the limbs. These nodules may ulcerate and either become inactive and heal by scarring or disseminate to cause indurated plaques covering the entire limb.

Disseminated Disease

This was commonly reported in patients with AIDS in the pre-ART era. Usually infection with *M. avium complex* occurred in children with congenital immunodeficiencies or *M. chelonae* in renal transplant recipients. But with emergence of HIV pandemic, disseminated NTM with *M. avium* or *M. genavense* was reported in around 30–40% of patients with AIDS. Children present with nonspecific symptoms like fever, weight loss, night sweats or anemia and the diagnosis is made by blood culture or lymph node or bone marrow biopsies.

DIAGNOSIS

Infection with NTM should be suspected in children with TB-like signs and symptoms, in whom initial antitubercular treatment or antibiotics have not produced the desired response. This should be supported by repeated isolation of the same NTM species from sputum, bronchoalveolar lavage or from the local lesion like lymph node or ulcers. The American Thoracic Society (ATS) recommends a combination of both clinical and microbiological criteria to diagnose pulmonary NTM disease.

Clinical (Both Required)

- Pulmonary symptoms, nodular or cavitary opacity in chest radiograph or HRCT scan that shows multifocal bronchiectasis with multiple small nodules and
- Appropriate exclusion of other diagnosis.

Microbiological

- Positive culture results from at least 2 separate expectorated samples or...
- Positive culture from at least one bronchial wash/lavage or...
- Transbronchial or other lung biopsy with mycobacterial histological feature [granulomatous inflammation or acid-fast bacilli (AFB)] and positive culture for NTM.

- Patients who are suspected of having NTM lung disease but do not meet diagnostic criteria should be followed until firm diagnosis is established or excluded.

There are no reference standards for laboratory diagnosis of NTM infection. Diagnosis is usually made on a combination of findings.

Culture of Nontuberculosis Mycobacteria

A definite diagnosis of NTM lymphadenitis is made by recovery of the causative organism from lymph node cultures. Cultures should include both solid and broth media for detection of mycobacteria and a semi quantitative colony count reporting is recommended. Most NTM grow within 2–3 weeks of subculture, while the rapid growers appear within 7 days of subculture. Failure of the lymph node culture to yield *M. tuberculosis* provides stronger presumptive evidence for the diagnosis of NTM lymphadenitis. However, the disease characteristics do not differ between children with positive culture from those without a positive culture.

Diagnosis of pulmonary NTM disease can be made by isolation and identification of causative organism in the sputum or the bronchoscopic specimens.

Identification of Nontuberculosis Mycobacteria Species

Currently there are multiple techniques for NTM species identification, including phenotypic, chemotaxonomy, nucleic acid probes, polymerase chain reaction and other amplification methods, high-performance liquid chromatography (HPLC) and nucleic acid sequencing. HPLC, which analyzes the chromatographic profile of the mycolic acids, extracted from the bacterial cell wall, speciates a large number of NTM. Identification of mycobacteria by sequencing of the 16S ribosomal RNA, which is highly conserved so that 1% or greater differences in this gene sequence can define an NTM species more accurately. DNA fingerprinting techniques have also been tried to identify the strains of NTM. In India, information on molecular types of NTM is scanty.

Sensitivity Profile

Drug susceptibility profile of NTM is usually very different from *M. tuberculosis*. Rapidly growing NTMs are usually resistant to rifampicin and isoniazid while they are sensitive to drugs like new generation macrolides and cephalosporin. In children with NTM lymphadenitis, besides negative tuberculin test and normal chest X-ray, the organisms will be resistant to antitubercular drugs.

Histopathological Examination

The diagnosis of NTM lymphadenitis is based on the histopathological appearance of the lymph node showing caseating granulomas with or without AFB. Histopathology is a useful method to diagnose *Mycobacterium avium complex* (MAC) infections of the lymph nodes especially when it is confirmed with an *in situ* method like antigen detection or gene probe.

Imaging Techniques

Imaging of the head and neck in immunocompetent children, using computed tomography (CT) or magnetic resonance imaging (MRI) scan would reveal asymmetric adenopathy with contiguous low-density ring-enhancing masses, similar to TB lymphadenopathy. Inflammatory stranding of the subcutaneous fat may also be seen. In case of pulmonary NTM disease, plain chest radiograph or high resolution computed tomography (HRCT) would demonstrate the characteristic abnormality of nodular/bronchiectatic NTM lung disease. There are no diagnostically reliable clinical and radiological differences between NTM lung disease and TB and, diagnosis depends on the isolation and identification of causative organism.

Diagnostic Skin Testing

Testing can be done with purified protein derivative (PPD) of *M. avium* (PPD-A), *M. scrofulaceum* (PPD-S) or *M. kansasii* (PPD-K) in addition to *M. tb* (PPD-B) that often shows cross-reactivity and culture and cytological/histological examination of aspirated or biopsy specimen. Skin testing is cheap and easy to perform. However, interpretation of skin test results is not accurate as there is cross reactivity between mycobacterial antigens.

Other Biomarkers

Cytokine/Chemokine signature of IL-5, IL-9, IL-13 and IL-17 have been identified as immunological biosignature to differentiate exposure to *M. avium* and *M. kansasii* in children from latent TB infection in areas where both TB and NTM are endemic, as in India.

TREATMENT

Making the diagnosis of NTM disease does not, per se, necessitate treatment. Treatment depends on the site and severity of the infection, the presence of predisposing condition, such as congenital or acquired immunodeficiency and the virulence of the mycobacterium species. The decision to treat should also be based on potential risk and benefit of therapy for individual patients.

All patients should receive long-term antimycobacterial therapy with double or triple drug regimens. These include various combinations of clarithromycin, ethambutol, rifabutin, rifampin, clofazimine, and azithromycin (**Table 2**). Skin lesions may be cured by excision, curettage or drainage. Surgical excision, when technically possible, is used to treat lymphadenitis or localized pulmonary nodules.

Treatment of Lymphadenitis

There is a lack of consensus about optimal treatment of NTM infection in otherwise healthy children. Spontaneous regression

may occur in a proportion of cases while chemotherapy, surgery or a combination of both may be required in others. Excisional surgery without chemotherapy is the recommended treatment for children with NTM cervical lymphadenitis, including those with disease caused by *M. avium complex* and *M. scrofulaceum*. Success rate with surgery is approximately 95%. Benefits of complete surgical excision include: a greater chance of isolating the causative organism; higher cure rates; faster healing times; less need for repeat surgical interventions and improved esthetic results. If surgical excision is not considered feasible, antimicrobial therapy may be considered for some patients. For children with recurrent disease, a second surgical procedure is usually performed.

An alternative for recurrent disease or for children in whom surgical risk is high (e.g., risk of facial nerve involvement with preauricular nodes) is chemotherapy, with one of the macrolides like clarithromycin showing some benefit. Cure with medical management alone generally requires prolonged antimicrobial regimens. Drug treatment is directed against MAC unless a different mycobacterial species has been isolated. Therapy of 3–6 months with clarithromycin or azithromycin combined with ethambutol or rifampin may be beneficial for those patients with incomplete surgical excision due to disease near the facial nerve or with recurrent disease as surgery may be associated with complications like damage to facial nerve branches when submandibular nodes are involved.

PROPHYLAXIS

Chemoprophylaxis with antimycobacterial drugs, such as rifabutin, has been recommended as primary prophylaxis in western countries for AIDS patients. However, we lack information on the role of chemoprophylaxis in children with HIV/AIDS in India.

Table 2 Treatment schedule of common nontuberculous mycobacterial species in India

Species	Regimen with dose	Duration and rhythm of treatment	Alternative regimen/Follow-up monitoring
<i>Mycobacterium avium</i> complex	Clarithromycin* 7.5 mg/kg (max 500 mg) BD + rifampicin 10 mg/kg (max 600 mg) OD + ethambutol 15 mg/kg (max 1.5 g) OD orally	Treatment will be daily for a minimum of 18 months or until they have been culture negative for a period of 12 months	Azithromycin (10 mg/kg—max 500 mg) OD orally instead of clarithromycin or rifabutin** (150–300 mg) instead of rifampicin
<i>Mycobacterium abscessus</i>	Clarithromycin 7.5 mg/kg (max 500 mg) BD orally + amikacin IV 30 mg/kg OD + ceftioxin (max 12 g/day) (or imipenem)	3-week intensive phase followed by a prolonged continuation phase, is recommended as first line therapy Surgical resection	Full blood count and the patient's renal and hepatic function must be checked prior to initiating treatment Renal and liver function should be checked at 12 weekly intervals
<i>Mycobacterium kansasii</i>	Isoniazid 5 mg/kg/day; (max 300 mg) + rifampicin 10 mg/kg/day (max 600 mg) + ethambutol 15 mg/kg (max 1.5 g) od orally	Daily for 12 months of negative sputum culture while on therapy	Clarithromycin, rifabutin and ethambutol can be used as alternative regimen
<i>Mycobacterium fortuitum</i>	Clarithromycin + Doxycycline + TMP-SFX or levofloxacin	12 months of negative sputum culture while on therapy	Avoid minocycline, doxycycline and tigecycline in patients less than 12 years of age
<i>Mycobacterium terrae</i>	Optimal therapy has not been established. Suggests use of a macrolide + ethambutol or other agent based on in vitro susceptibility test		
<i>Mycobacterium chelonae</i>	Optimal therapy is still unknown. Suggested regimen including clarithromycin with a second agent (based on in vitro susceptibility) for 12 months of negative sputum cultures		
<i>Mycobacterium scrofulaceum</i>	Susceptibility data are lacking and standard treatment regimens is still controversial		

*The superiority of clarithromycin over azithromycin not demonstrated in trials.

**Most experts recommend rifampicin because of frequent adverse events with rifabutin.

IN A NUTSHELL

1. Atypical mycobacteria can affect both immunocompromised as well as immunocompetent individuals.
2. There is no evidence of animal-to-animal or human-to-human transmission of NTM. Human disease is presumably acquired from environmental exposure, though a specific source may be difficult to identify.
3. Infection with NTM should be suspected in children with TB-like signs and symptoms, in whom initial antitubercular treatment or antibiotics have not produced the desired response.
4. Cervical lymphadenitis is the most common form of NTM disease in children.
5. Making the diagnosis of NTM disease does not, per se, necessitate treatment. Treatment depends on the site and severity of the infection, virulence of the mycobacterium species and should also be based on potential risk and benefit of therapy for individual patients.

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Chapter 30.4

Leprosy

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Leprosy, also known as Hansen disease, is a chronic infection caused by the bacteria *Mycobacterium leprae*. It particularly affects peripheral nerves, skin, and mucous membranes in the cooler parts of the body, such as the upper respiratory tract, anterior chamber of the eye, and the testes.

EPIDEMIOLOGY

According to WHO, out of a total 232,857 registered cases of leprosy in the world in 2012, 125,171 (9.82% children) were residing in India. The prevalence rate decreased in last decade globally from 1.6/10,000 population in 1997 to 0.34/10,000 population in 2012.

Leprosy is widely prevalent in India. After introduction of MDT the total number of registered cases of leprosy came down to less than 0.1 million (prevalence rate of 0.66/10,000 population) in 2012 from 0.5 million (prevalence rate of 6.7/10,000 population) in 1997. The total number of new cases detected during 2012 in India was 166,445; of these, about 10% were children below 15 years of age.

ETIOLOGY

Leprosy is caused by *M. leprae* which is an acid-fast, nonsporing bacilli, and occurs both intracellularly as well as extracellularly. In stained smear it lies singly, as rods or in clumps called globi (Fig. 1). They have affinity for Schwann cells and cells of reticuloendothelial system. The bacillus cannot be grown in any artificial media. *M. leprae* does not produce any toxin and is well adapted to reside within macrophages, yet it may survive outside the body for months.

MODE OF TRANSMISSION

The only source of infection is the infected human being. The capacity of multibacillary leprosy patients to infect is 4–11 times that of patients with paucibacillary leprosy. The mode of transmission of leprosy has not been established with certainty.

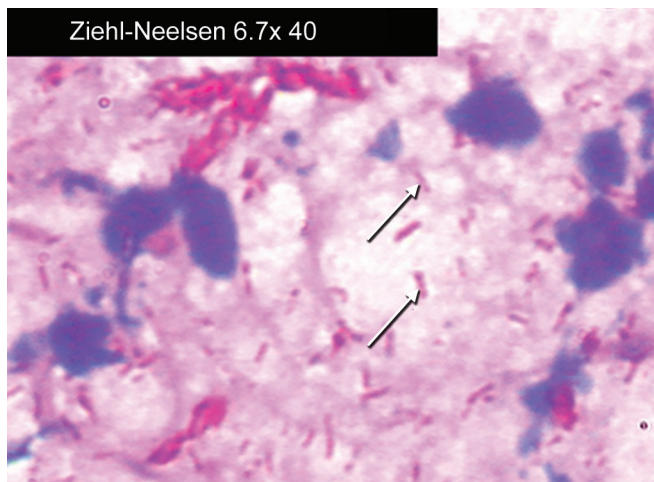


Figure 1 Smear microscopy by Ziehl-Neelsen staining

Direct Transmission

For direct transmission, a prolonged and close contact is required. An intrafamilial contact with a patient is more risky than an extra-familial one. Untreated, lepromatous patients discharge as many as 100 million bacilli from their nasal secretions every day. These bacilli remain viable outside the human body for several days. Inhalation of these droplets is now regarded as the most common mode of entry of bacilli into contact person. After inhalation, these inhaled bacilli enter the respiratory system from where they are disseminated by blood to skin and peripheral nerves. Bacilli may also be transmitted by insect vectors, tattooing needles, or by ingestion of infected breastmilk. Through this abraded skin, the droplets laden with leprosy bacilli enter through the epidermis into the dermis.

Indirect Transmission

M. leprae remains viable for several days outside the human body. Occasionally, bacilli may be transmitted from person to person by close contact between an infectious patients and healthy but susceptible person. This contact may be direct or indirect (e.g., contact with soil and fomites such as contaminated clothes and linen).

CLINICAL MANIFESTATIONS

Incubation Period

Owing to the extremely slow dividing time of *M. leprae* (once every 2 weeks) the incubation period ranges from 6 months to more than 40 years and averages 2–5 years.

Clinical Features

Leprosy is primarily a granulomatous disease of the peripheral nerves and mucosa of the upper respiratory tract; skin lesions are the primary external sign. Left untreated, leprosy can be progressive, causing permanent damage to the skin, nerves, limbs and eyes. The age group most commonly affected is 5–14 years, though in very high endemic countries, prevalence in age groups 0–4 years is also significant. The early signs include:

- A hypopigmented patch in the skin, present for a long duration, nonirritating with loss of sensation to touch, pain and temperature
- Thickening of the skin, more red and shiny in appearance than surrounding parts; this is more prominent on face and hands
- Loss of sensation, numbness, feeling of pins and needles or crawling of ants, tingling sensation in any part of body
- Appearance of spontaneous blisters and ulcers, especially in the fingers.

CLASSIFICATION

Leprosy is classified into several types based on the bacterial load present in the lesions, the extent of skin and nerve involvement and based on the presence of deformities. Several types of classification exist like Madrid classification, Ridley and Jopling classification Indian classification, WHO classification, and Field Worker's Classification. According to the classification (1981) laid down by Indian Leprosy Association (*Hind Kusth Nivaran*), the cases are categorized into five broad groups *viz.*, indeterminate, borderline, tuberculoid, lepromatous and polyneuritic.

Indeterminate Leprosy

This type is seen in only 10–20% of infected individuals and is earliest detectable form of leprosy. This is characterized by presence of one or two vague hypopigmented macules and definite sensory impairment. The macule is of 2–4 cm in diameter, with

poorly defined border without any erythema or induration. The lesions are bacteriologically negative.

Tuberculoid Leprosy

Tuberculoid leprosy (TT) denotes those cases with single or few well-defined, hypopigmented, erythematous or copper-colored patches, and are anesthetic. The entire patch or only its margin is raised above the level of the surrounding skin. Initially, a single nerve trunk related to the lesions is affected. The nerve trunk becomes enlarged, hard, tender and later may form a nerve abscess. In this form, lepromin test is positive and there is absence of bacilli in skin smear. On biopsy, foci of lymphocyte, epithelioid cells and Langhans giant cells are seen. This form of leprosy is the most common, especially in children and is relatively benign and stable with a good prognosis.

Borderline Leprosy

It is further classified into three subtypes:

Borderline Tuberculoid Leprosy

In borderline tuberculoid (BT) leprosy the lesions are greater in number but smaller in size than in TT. There may be small satellite lesions around older lesions and the margins of the BT lesions are less distinct and the center is less atrophic and anesthetic. This form usually involves thickening of two or more superficial nerves.

Mid-borderline Leprosy

In mid-borderline (BB) leprosy the lesions are more numerous and heterogeneous. The lesions may become confluent or even plaques may be present. The borders are poorly defined and the erythematous rim fades into the surrounding skin. Hyperanesthesia is more common than anesthesia.

Borderline Lepromatous Leprosy

In borderline lepromatous (BL) leprosy there are a large number of asymmetrically distributed lesions which are heterogeneous in appearance. Macules, papules, plaques and nodules may all coexist. Mild anesthesia with sparing can be present.

Neuritic Leprosy

This type denotes those cases which show nerve involvement but do not have any lesions in the skin. This may be primary or secondary variety. The affected nerves become thickened and tender, producing sensory, motor and trophic changes in their area of distribution. This dysfunction leads to deformities, neuropathic ulcers and lagophthalmos which may result in serious eye complications. The common nerves involved are ulnar, lateral popliteal, tibial, greater auricular and rarely radial nerve. It can also affect fifth and seventh cranial nerves.

Lepromatous Leprosy

Most cases of lepromatous leprosy (LL) develop from borderline leprosy. This form is relatively uncommon in pediatric age group. There are two symptoms, which may precede the classical lesions by months or years, and serve to alert the physician to a possible early diagnosis: (a) nasal symptoms—stuffiness, crust formation, blood-stained discharge; and (b) edema of legs—always bilateral, prominent late in evening and which disappears after overnight rest. Skin lesions are diffusing infiltrated or numerous flat or raised, poorly defined, coppery, shiny, smooth, symmetrically distributed. Patients may have a leonine face due to loss of eyebrows and eyelashes. There is no sensory impairment in these lesions but as the disease progresses many peripheral nerves get symmetrically affected. These lesions are bacteriologically positive. The lepromin

test is negative. This form is most infectious, prone to lepra reaction and if left untreated, the prognosis is poor (Fig. 2).

Differential features of various types of leprosy are compared in Table 1.

DIAGNOSIS

Diagnosis of leprosy is based on the presence of any one of the following cardinal signs:

- Characteristic skin lesion with partial or total loss of sensation in the affected skin lesion
- Presence of acid fast bacilli in the skin smear.

Bacteriological Examination

Skin smears are useful for diagnosing multibacillary leprosy and were originally used for distinguishing between paucibacillary and multibacillary leprosy. If no definite patches or areas of thickened skin are visible, smear should be taken from ear lobules and buttocks. Smear should be made by “slit and scrape” method and stained by Ziehl-Neelsen staining. Smears are positive in LL, BL and some BB and some BT cases. It is of limited help in TT and indeterminate lesions and patients with early atypical clinical presentation. In some cases of indeterminate lesion it becomes necessary to carry out a histological examination for the purpose of diagnosis and classification of the lesion.

Bacterial Index

Bacterial index (BI) is the only objective way of monitoring the benefit of treatment. It is a semiquantitative estimation of the density of bacilli present in the skin smears and biopsies and is measured on two scales, namely the Dharmendra scale and Ridley scale. It ranges from zero to 6+ and is based on the number of bacilli (live and dead) seen in an average microscopic field of the smear using an oil immersion objective. Patients are labeled as having paucibacillary infection when there are less than or equal to 5 skin lesions. They are labeled as having multibacillary infection when there are more than or equal to 6 skin lesions. The BI can range from 0 (No bacilli in 100 oil immersion field) to 6 (more than 1000 bacilli per field).

Foot Pad Culture

Inoculation of material into the mouse foot pad is the only certain way to demonstrate the multiplication of bacilli. This method is 10 times more sensitive at detecting *M. leprae* than are slit skin smear.



Figure 2 A child with borderline lepromatous leprosy

Table 1 Differential features of various types of leprosy

Features	Types of leprosy				
	TT	BT	BB	BL	LL
Number of lesions	Single usually	Single or few	Several	Many	Very many
Size of lesions	Variable	Variable	Variable	Variable	Small
Surface of lesions	Very dry, sometimes scaly	Dry	Slightly shiny	Shiny	Shiny
Sensation in lesions	Absent	Markedly diminished	Moderately diminished	Slightly diminished	Not affected
Hair growth	Absent	Markedly diminished	Moderately diminished	Slightly diminished	Not affected
AFB in lesions	Nil	Nil or scanty	Moderate numbers	Many	Very many (plus globi)
AFB in nasal scrapings/ in nose blows	Nil	Nil	Nil	Usually nil	Very many (plus globi)
Lepromin test	Strongly positive (+++)	Weakly positive (+ or ++)	Negative	Negative	Negative

Abbreviations: AFB, acid fast bacilli; TT, tuberculoid; BT, borderline tuberculoid; BB, mid-borderline; BL, borderline lepromatous; LL, lepromatous leprosy.

Immunological Methods

These include tests for detecting cell-mediated immunity (CMI) as discussed below:

Lepromin Test

This is a test using intradermal injection of 0.1 mL of lepromin (Dharmendra or Mitsuda antigen) into the inner aspect of forearm of the individual. The reaction is read at 48 hours and 21 days to classify the stage of leprosy based on the lepromin reaction (Fernandez or Mitsuda reaction). It differentiates TT and BT, in which there is a positive delayed reaction at the injection site, from LL and BL, in which there is no reaction (a negative test result) despite the active malignant *M. leprae* infection. This test is not diagnostic, because normal uninfected people may also react. This test signifies immunity of a person, i.e., cell-mediated immunity against *M. leprae* or its antigen.

Serological Assays

These tests are expected to have value in detecting subclinical infections and in assessing efficacy of drug treatment. *Fluorescent leprosy antibody absorption test* (FLA-ABS) is used for identification of subclinical infection and is useful in identifying healthy contacts of patients. This test is 92% sensitive and 100% specific in detecting *M. leprae* specific antibody. *Radioimmunoassay* detects antibody to the cell wall antigens of *M. leprae*. Monoclonal antibodies against *M. leprae* antigens have been produced. These antibodies recognize specific and nonspecific epitopes of *M. leprae* antigens. An antibody competition test, sickle cell anemia test (SCAT) based on this approach has been found to be sensitive for detection of *M. leprae* antibody. Also, enzyme-linked immunoassays (ELISA) were found highly positive in multibacillary cases, but positivity in paucibacillary and subclinical case was quite low. Further simplified dot ELISA and dipstick ELISA using a monoclonal antibody targeting phenolic glycolipid-1 (PGL-1) have also been studied. Serological testing is not useful for diagnosis as it does not detect most paucibacillary cases and it remains positive even after treatment of multibacillary patients.

Molecular Biological Approaches

Identification of organisms can be done in a more rapid and specific way, both from culture and directly from clinical specimen, by recombinant DNA technology. Based on gene sequences of *M. leprae*, several probes have been designed in recent years.

Several gene amplification techniques, polymerase chain reaction (PCR) for amplifying *M. leprae* specific sequences from variety of specimens have been published and reported to be highly sensitive and specific.

In situ PCR, with the added advantages of providing structural correlates and permitting concomitant study of tissue pathology, improves the diagnostic yield especially in early and doubtful cases of leprosy where the histopathology is nonspecific. In situ hybridization improves the diagnostic yield significantly. In situ PCR on slit skin smear has an average positivity of 72%, better than that on skin biopsy (60%). In addition it has the added advantage of being minimally invasive and less cumbersome and can be performed even at sites from where skin biopsy is difficult. Another latest in our series in 2013 proved that *M. leprae*-specific repetitive element (RLEP) based PCR on slit skin smear is a useful tool to confirm early cases of leprosy, where skin smears are negative. It was found positive in 72% cases while skin smears only in 18% of cases.

TREATMENT

Leprosy patients should be treated with patience, perseverance and understanding. Besides the medical treatment, the patients and their parents need moral support and reassurance. Parents should be explained hygienic measures, proper diet and importance of taking treatment completely and regularly.

Multidrug Therapy

It is now a well-known fact that, simultaneous administration of several different antibacterial agents may prevent the emergence of drug resistant mutants.

The standard child (ages 10–14 years) treatment regimen for multibacillary (MB) leprosy is:

Rifampicin—450 mg once a month
Clofazimine—150 mg once a month and 50 mg every other day
Dapsone—50 mg daily
Duration—12 months

The standard child (ages 10–14 years) treatment regimen for paucibacillary (PB) leprosy is:

Rifampicin—450 mg once a month
Dapsone—50 mg daily
Duration—6 months

The dosage schedule for children below 10 years as recommended by WHO, is shown in **Table 2**.

Table 2 WHO multidrug therapy regimens

Type of leprosy	Daily, self-administered	Alternate day, self-administered	Monthly, supervised	Months of treatment
Paucibacillary	Dapsone 2 mg/kg	—	Rifampicin 10 mg/kg	6
Multibacillary	Dapsone 2 mg/kg	Clofazimine 1 mg/kg	Rifampicin 10 mg/kg, Clofazimine 6 mg/kg	12

Source: WHO, Leprosy elimination, <http://www.who.int/lep/mdt/en/>, accessed March 14, 2013

In the MDT, it is assumed that clofazimine is acceptable for children and, therefore, no child will require ethionamide/prothionamide which are potent hepatotoxic drugs. Parents should be advised to give rifampicin on empty stomach and clofazimine with meals or with a glass of milk.

Treatment of Reactions

Drugs commonly used in these conditions are antimalarials (chloroquine), antimonials, clofazimine, corticosteroids and thalidomide. Symptoms such as iritis and neuritis occurring during reactions (or occurring independently) should be properly treated in order to avoid irreversible sequelae, i.e., deformities and neuropathic ulcers.

Duration of Therapy

- Paucibacillary leprosy—PB blister packs for 6 months.
- Multibacillary leprosy—MB blister packs for 12 months.

PREVENTION

Household contacts of patients with LL, especially children, should be monitored annually for 5 years following diagnosis. Chemoprophylaxis with dapsone is no longer recommended. Various attempts have been made to develop a vaccine against leprosy, with the BCG vaccine having mixed results; other vaccines under development or being explored are the *Mycobacterium w*, *Mycobacterium* ICRC, and BCG plus heat-killed *Mycobacterium* species vaccines. A meta-analysis of 7 experimental studies and 19 observational studies found that the overall protective effect of the BCG vaccine was 26% in the experimental studies and 61% in the observational studies.

IN A NUTSHELL

1. Leprosy is a chronic disease caused by a slow multiplying bacillus, *M. leprae* with a long incubation period of 2–5 years.
2. The disease mainly affects the skin, peripheral nerves, mucosa of the upper respiratory tract and also the eyes.
3. Although not highly infectious, it is transmitted via droplets, from the nose and mouth, during close and frequent contacts with untreated cases.
4. With the help of newer diagnostic modalities, early diagnosis and treatment with MDT is possible and remains the key in eliminating the disease.
5. Leprosy is curable.
6. In WHO MDT rifampicin, clofazimine and dapsone are used for MB leprosy while rifampicin and dapsone for PB leprosy. Treatment should be continued for 6 months in PB leprosy and 12 months in MB leprosy.
7. Untreated leprosy can cause progressive and permanent damage to the skin, nerves, eyes and limbs.

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Section 31 VIRAL DISEASES

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Chapter 31.1

Epidemiology of Viral Infections

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To cause infection, viruses must gain entry into the body, multiply, and spread, either locally or systemically; and in the generalized infections, localize in the appropriate target organ. To be maintained in nature, infectious virions must be liberated or released in the environment, or taken up by an arthropod vector, a needle, or passed congenitally.

ROUTE OF ENTRY

Respiratory Tract

Respiratory tract is the most important entry site for the virus to enter the body. Particles 10 μm or more in diameter are usually deposited on the nasal mucosa over the turbinate bones, which project into the nasal cavity and act as baffle plates. Particles 5–10 μm in diameter may be carried to the trachea and bronchioles, where they are usually trapped in the mucus blanket. Particles of 5 μm or less are usually inhaled directly into the lungs, and some may reach the alveoli, where the virus may infect alveolar epithelial cells or be destroyed by alveolar macrophages.

All viruses that infect a host via the respiratory tract probably do so by attaching to specific receptors on epithelial cells. Following respiratory infection, the virus remains localized (e.g., rhinoviruses, parainfluenza and influenza viruses) or spread systemically (e.g., measles, chickenpox and rubella viruses).

Alimentary Tract

Many viruses are acquired by swallowing. They infect cells in the oropharynx and are then carried to the intestinal tract. The esophagus is rarely infected, probably because of its tough stratified squamous epithelium, and rapid passage of swallowed material over its surface. Virions can attach to specific receptors in the intestines or may be taken up by the specialized M-cells overlying Peyer patches in the ileum. Acid, bile and proteolytic enzymes in the gastrointestinal cells may inactivate viruses. Therefore, most of the viruses that cause intestinal infections, such as enteroviruses and rotaviruses are acid and bile resistant. Some of the enteroviruses (e.g., polio viruses), and hepatitis A and E viruses are important causes of generalized infection but do not produce signs pertaining to the intestinal tract.

Skin

Viruses entering through the skin may replicate in the skin itself to produce local lesions (e.g., papilloma viruses and pox viruses). They may enter the skin through the bite of an arthropod vector, such as a mosquito, tick or sandfly. Such viruses are called *arboviruses*. Infections can be acquired through the bite of an animal, as in rabies and iatrogenically as in the transmission of hepatitis B, C and

HIV, by contaminated needles or blood transfusion. Generalized infection of the skin, producing an exanthem such as found in measles, chickenpox, rubella and general arbovirus diseases, is due to viral dissemination through the bloodstream.

Other Routes

Herpes simplex viruses and papilloma viruses enter through the genital tract and produce lesions locally on the genitalia and perineum. HIV, human T-lymphotropic virus, and hepatitis B and C viruses may also enter through the genital tract but do not produce local lesions. Conjunctiva is a rare route of entry for some adenoviruses and a few enteroviruses.

MECHANISMS OF SPREAD

Viruses may remain localized to the body surface through which they entered—skin, respiratory tract, gastrointestinal tract, genital tract, or conjunctiva—or cause generalized infections associated with viremia and subsequent localization in particular organs.

Local Spread

On epithelial surfaces Papilloma viruses replicate in epithelial cells of skin at the site of entry, producing a localized or spreading infection in the epithelium by sequentially infecting the neighboring cells. Viruses that enter the body via the intestinal tract or respiratory tract usually have a short incubation period and usually do not invade beyond the epithelium, because the temperature of deeper tissues is higher than the optimal temperature for viral replication, though these viruses have the potential to spread (e.g., paramyxoviruses, influenza viruses and the rotaviruses).

Subepithelial invasion and lymphatic spread Virions that enter lymphatics in the subepithelium are carried to local lymph nodes and initiate an immune response. Some virions may pass straight through lymph nodes to enter the bloodstream. The extent of local inflammatory response depends on the extent of tissue damage.

Viremia

Once a virus has reached the bloodstream, usually via the lymphatic system, it can localize in any part of the body within minutes. The first entry of the virus into the blood is called *primary viremia*; this early viremia may be clinically silent. Further replication in these sites leads to the sustained liberation of much higher concentrations of virus, producing a *secondary viremia*, which in turn can lead to the establishment of infection in other parts of the body (usually liver, spleen, lymph nodes and bone marrow) and clinical symptoms.

Invasion of Skin

The skin may be invaded via the bloodstream producing erythema, and often a generalized macular, papular, vesicular or pustular rash. More severe involvement of the dermal vessels may lead to petechial or hemorrhagic rashes.

Invasion of Central Nervous System

Viruses can spread from the blood to the brain either: (1) after localizing in the blood vessels of the meninges and choroid plexus—invading the neurons from the cerebrospinal fluid; or (2) directly after localizing in blood vessels of the brain and spinal cord. Subsequent spread in the CNS can take place via the cerebrospinal fluid or by sequential infection of neural cells.

Another important route of viral infection of the CNS is via the peripheral nerves as seen in rabies, varicella and herpes simplex. Viruses may pass (1) either centripetally from the body surface to the sensory ganglia; or (2) centrifugally from the ganglia to the skin—the reactivation of herpes simplex or varicella—as zoster. The rate of travel is quite slow, at 10 mm per hour. Rabies virus infection though considered lethal, is noncytotoxic; it evokes little of the inflammatory reaction or cell necrosis, characteristic of herpes or poliovirus encephalitis. Post infectious encephalitis is most commonly seen after measles, mumps, rubella and varicella and is thought to be an autoimmune process rather than a direct result of a virus infection. Some of the viruses or virus like agents cause slow progressive diseases of the CNS and characteristic pathologic changes. These virus like agents are known as *prions* (causative agents of Creutzfeldt-Jakob disease, Kuru).

Invasion of Other Organs

Most viruses exhibit a well-defined organ and tissue tropism. The most dangerous viral infections tend to be those that cause encephalitis, pneumonia, carditis, hepatitis, or hemorrhagic fever. Infection of the sexual organs may lead to excretion of the virus in genital fluids and risk of transmission during sexual activities. Similarly, localization of virus in the salivary glands (e.g., mumps), mammary glands, kidney tubules, and lungs leads to excretion of the virus in the saliva, milk, urine, and respiratory secretions respectively. Maternal rubella and cytomegalovirus contracted in the early months of pregnancy often leads to multiple congenital abnormalities in the baby including deafness, blindness, congenital heart defects and developmental delay.

MAINTENANCE OF VIRUS IN NATURE

Shedding of the infectious virions is necessary to maintain the infection in the population; it usually occurs from one of the body openings or surfaces that are involved in both entry and exit. In generalized infections several modes of shedding are recognized: for example, hepatitis B virus, HIV, cytomegalovirus are shed in semen, cervical secretions, milk and saliva. The amount of virus shed in an excretion or secretion is important in relation to its transmission. Very low concentrations may be irrelevant unless very large volume of infected material is transferred. On the other hand, some viruses occur in such high concentrations that a minute quantity of material, for example, less than 5 μ L, can transmit infection.

Respiratory or Oropharyngeal Secretions

Viruses causing respiratory tract illnesses are shed in mucus, saliva or expelled during coughing, sneezing and talking. They are also shed from the respiratory tract in several systemic infections, such as measles, chickenpox and rubella. A few viruses, for example, the herpes viruses, cytomegalovirus and EB virus, are shed into the oral cavity from infected salivary glands, or from the lung or nasal mucosa and transmitted by salivary exchange in kissing and other social activities.

Feces

Enteric viruses are shed in the feces; the more voluminous the fluid output, the greater is the environmental contamination they cause.

Generally, they are more resistant to inactivation by environmental conditions than the enveloped respiratory viruses.

Skin

The skin is an important source of virus in diseases where transmission is by direct contact; for example, molluscum contagiosum, warts and genital herpes. Several pox viruses may be spread from animals to humans and sometimes from humans to animals by contact with skin lesions. Virus is not shed from the maculopapular skin lesions of measles, flavivirus or picornavirus infections. Herpes virus infections produce vesicular lesions in which the virus can be isolated in plenty. Even here, however, the virus shed in saliva and aerosols is much more important, as far as transmission is concerned, than that shed via the skin lesions.

Breastmilk

Several viruses, for example cytomegalovirus and HIV, are excreted in milk, which may serve as a route of transmission to the newborn infant.

Genital Secretions

Many viruses can be found in semen or vaginal secretions. They include HIV, herpes viruses, hepatitis B and C viruses.

Blood

Blood is the usual source from which arthropods acquire viruses—by inserting their proboscis into a capillary. Blood may also transfer viruses to the ovum or fetus. Hepatitis B, C and D viruses, and HIV can be spread by blood transfusion and contaminated needles.

No Shedding

Certain organs such as brain, which are not accessible to the external environment directly, are not conducive for viral shedding. For sustenance of the virus in nature, these sites of viral replication contribute little. Nevertheless, quantal increase in virus titer in such organs may be relevant for shedding to occur from a different site or for infection of blood sucking vectors.

IN A NUTSHELL

1. Viruses can enter the human body through inhalation, ingestion, infection into the skin, sexual contact and conjunctiva.
2. To be maintained in nature, the virus must be again liberated in the environment, or taken up by an arthropod vector, a needle, or transmitted transplacentally.
3. After entering the host, virus can remain localized to that area or disseminate through blood (viremia). Viremia may spread the virion to localize in particular organs.
4. Viruses can cause mild to severe illnesses, ranging from common cold to encephalitis, carditis, immune suppression, or hemorrhagic fevers.

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Chapter 31.2

Poliomyelitis

Ashok Kumar Dutta

Poliomyelitis is a highly infectious, crippling, and often fatal disease, caused by any of the three serotypes of poliovirus, which mainly affects children under five years of age. It is most often recognized by acute onset flaccid paralysis of the limbs. The condition was considered in the past as one of the most feared infectious disease because of the permanent residual paralysis and disability. However, with the intelligent use of the available polio vaccines, the disease has become a rarity with only three countries of the world, e.g., Pakistan, Afghanistan and Nigeria as the only endemic countries in the world. However, there is always threat of spread of the disease from these countries and in 2013–14 several countries in African horn were affected with fresh cases of poliomyelitis from Nigeria. At present vaccine-associated paralytic poliomyelitis (VAPP) and vaccine-derived poliovirus (VDPV) are occurring in many countries. World Health Organization (WHO) aims at global eradication of both wild as well as vaccine virus causing poliomyelitis.

EPIDEMIOLOGY

Poliovirus is highly communicable disease for which human is the only reservoir. It multiplies in the intestine and is spread via fecal-oral route. The average incubation period is 7–10 days (range 4–35 days). The maximum excretion of virus occurs just before the onset of paralysis and during the first 2 weeks after the onset of paralysis. However, the virus is excreted intermittently for up to 2 months after infection. Polio cases have decreased by over 99% since 1988, from an estimated 350,000 cases to less than 100 in 2014 globally. In 2014, only three countries (Afghanistan, Nigeria and Pakistan) in the world remain polio-endemic.

ETIOPATHOGENESIS

Poliomyelitis is caused by three antigenically distinct serotypes (type 1, 2 and 3) of polioviruses. The polioviruses are nonenveloped, positive-stranded RNA viruses and belong to the genus *Enterovirus* in the family Picornaviridae. These viruses can remain active for several days at room temperature and can be stored indefinitely frozen at -20°C . It is rapidly inactivated by heat, chlorine and ultraviolet light. The most frequent causes of epidemic polio are poliovirus type 1 followed by type 3. Wild type poliovirus type 2 was eradicated from the world in 1999. Following eradication of poliovirus from most part of the globe with oral polio vaccine (OPV), there is emergence of VAPP and VDPV, which is now leading cause of acute flaccid paralysis (AFP).

Polioviruses infect cells by adsorbing to specific genetically determined receptors. The primary site of replication is small intestine and regional lymph nodes. Poliovirus which probably accesses the CNS through peripheral nerves primarily infects motor neuron cells in the spinal cord (the anterior horn cells) and the medulla oblongata. Infants born to mothers with antibodies are protected naturally against paralytic polio for a few weeks. Active immunity after natural infection (including inapparent and mild infection) is probably lifelong but protects against the infecting serotype only. Therefore polio immunization is necessary even after an attack of poliomyelitis to prevent from other serotypes.

CLINICAL MANIFESTATIONS

In 90–95% of infected individuals, poliovirus infection is inapparent. In the remaining 5–10%, one of three syndromes may occur.

Abortive polio occurs in 4–8% of infections and is characterized by a minor illness with low grade fever, sore throat, vomiting, abdominal pain, loss of appetite, and malaise. Recovery is rapid and complete; there is no paralysis.

Nonparalytic polio occurs in 1–2% of infections and is characterized by headache, neck, back and leg stiffness which occurs several days after the prodrome (fever, malaise, etc.). Presentation resembles other causes of aseptic meningitis and recovery occurs within 2–10 days.

Paralytic polio occurs in 0.5–1% of infections (i.e., one case of paralysis in every 100–200 infected children). Symptoms often occur in two phases, minor and major, and are often separated by several days without symptoms. The minor phase consists of symptoms similar to those of abortive poliomyelitis. The major phase of illness begins with muscle pain, spasms and the fever. This is followed by rapid onset of flaccid paralysis that is usually complete within 72 hours. There are three types of paralytic poliomyelitis:

1. *Spinal paralytic poliomyelitis* is the most common form of paralytic poliomyelitis, seen in approximately 80% of paralytic cases. It results from a lower motor neuron lesion of the anterior horn of the spinal cord and affects the muscles of the legs, arms and/or trunk. The affected muscles are flaccid (lower motor neuron type) and reflexes are diminished. There is no sensory involvement. Paralysis is often asymmetrical, affecting legs more often than arms. Paralytic manifestation in extremities begin proximally and progress to involve distal muscle groups (i.e., descending paralysis). Severe cases may develop quadriplegia and paralysis of the trunk, abdominal and thoracic muscles. Residual flaccid paralysis is usually present after 60 days.
2. *Bulbar polio* accounts up to 2% of paralytic cases and results from a cranial nerve lesion, resulting in respiratory insufficiency and difficulty in swallowing, nasal regurgitation and difficulty in phonation.
3. *Bulbospinal polio* accounts for approximately up to 20% of paralytic cases which is a combination of both spinal and bulbar component.

Residual paralysis As the acute phase of illness (0–4 weeks) subsides, the recovery begins in paralyzed muscles. The extent of recovery is variable depending upon the extent of damage caused to the neurons by the virus. Maximum neurological recovery of the paralyzed muscle takes place in the first 6 months of the illness but slow recovery continues up to 2 years. After 2 years, no more recovery is expected and the child is said to have “Postpolio residual paralysis”, which remains as such throughout life.

Postpolio syndrome In some individuals it has been observed that there is clinical deterioration amongst survivors after several decades. There is recent muscle weakness, poor endurance, fatigue and muscle and joint pain. Exact pathogenesis of the syndrome is not known but is attributed to be a combination of ageing process and distal muscle degeneration due to the increased metabolic demand.

Vaccine-associated paralytic poliomyelitis (VAPP) In some of the recipient of OPV in less than 1% genetic changes in VP1 gene of vaccine virus takes place and the vaccine virus becomes virulent and causes paralysis in the same recipient or among close contacts who is not immune. Approximately one case of VAPP occurs after 2.3 million of first doses and after 12 million subsequent doses.

Table 1 Differential diagnosis of paralytic (acute flaccid) poliomyelitis

Signs and symptoms	Poliomyelitis	GBS	Transverse myelitis	Traumatic neuritis
Fever at onset	High, present	Not common	Rarely present	Present
Flaccidity	Asymmetrical and proximal	Symmetrical and distal	Symmetrical lower limbs	Asymmetrical limb
DTR	Decreased or absent	Absent	Absent in LL early hyper-reflexia late	Decreased or absent
Sensation	Myalgia, no sensory loss	Cramps, tingling hypoesthesia of palms and soles	Loss of sensation with sensory level	Pain in gluteal region
Cranial nerves involvement	Only in bulbar and bulbospinal	Often present VII, IV, X, XI, XII	Absent	Absent
CSF, WBCs	Increased	< 10 WBCs	Normal	Normal
CSF, protein	Slight increase	High	Normal or slight increase	Normal
Bladder dysfunction	Absent	Transient	Present	Never
Nerve conduction velocity—third week	Abnormal Anterior horn cell disease	Abnormal demyelination	No diagnostic value	Abnormal in sciatic nerve
EMG-third week	Abnormal	Normal	Normal	Normal

Abbreviations: GBS, Guillain-Barré syndrome; DTR, deep tendon reflexes; LL, lower limb; CSF, cerebrospinal fluid; WBC, white blood cells; EMG, electromyography.

According to WHO, approximately 500 cases are reported every year. VAPP is clinically indistinguishable from paralysis due to wild poliovirus.

Vaccine-derived poliovirus (VDPV) It is derivative of Sabin strain from OPV which exhibits about 1–15% genetic changes in the VP1 gene and usually transmits disease to nonimmune individual. The strain has potential for human infection and paralysis including sustained circulation and spreading disease in other countries through human travel and is a serious threat to spread of the disease in various countries of the world. In the last 5 years more than 500 cases of circulating vaccine-derived poliovirus (cVDPV) type 2 diseases have occurred in various countries which were declared polio free. This mutant strain is of three types:

Circulating vaccine-derived poliovirus (cVDPV) This emerges in areas with poor OPV coverage and chances of sustained person to person spread. WHO considers cVDPV as serious threat to polio eradication process.

Immunodeficient-associated VDPV (iVDPV) This strain is isolated from persons with primary immune deficiency states who exhibit prolonged infection after OPV exposure. These strains can persist for over 20 years.

Ambiguous vaccine-derived poliovirus (aVDPV) This strain is clinical isolate from nonimmunocompromised individual or environmental isolation from unidentified source.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of abortive and nonparalytic polio includes other viral fevers. Paralytic poliomyelitis needs differentiation from other causes of AFP. Paralytic poliomyelitis, Guillain-Barre syndrome, traumatic neuritis and transverse myelitis represent the most common causes of AFP, but the complete differential diagnosis includes numerous etiologies (hypokalemia, encephalitis, meningitis and other enterovirus infections, polymyositis, peripheral neuritis, myasthenia and other myopathies, etc.). Distinguishing characteristic of paralytic polio are asymmetric, AFP, mostly involving proximal muscles with fever and muscular pain at onset, rapid progression from onset to maximum paralysis (usually < 4 days), intact sensory nerve function, and most

often, residual paralysis or weakness after 60 days. Salient features of differentiation are summarized in **Table 1**.

DIAGNOSIS

Clinical Diagnosis

Characteristic clinical presentation of acute lower motor neuron type of asymmetrical paralysis of proximal limb muscles without any sensory involvement is highly suggestive of poliomyelitis. However, all cases of AFP cases should be investigated by sending a stool sample for isolation of virus.

Stool for Virus Isolation

Virus can be found in the feces from the onset to up to 8 or more weeks after paralysis, with the highest probability of detection during the first 2 weeks after onset. Isolation of wild poliovirus from stool is the recommended method for laboratory confirmation of paralytic poliomyelitis. Two stool specimens are collected from each case for laboratory confirmation. Adequate stool specimen is defined as two specimens collected at least 24 hours apart within 14 days of onset of paralysis. Each sample should have volume (8–10 g or thumb size) and sent to a WHO accredited laboratory in good condition with no desiccation, leakage and maintaining cold chain.

TREATMENT

The aim of treatment is to promote recovery, and to minimize residual muscle paralysis and disability. Treatment of the child with paralytic poliomyelitis varies with stage of illness and the severity of paralysis. Children with bulbospinal polio and respiratory paralysis would require hospitalization. In acute stage children with isolated limb/limbs paralysis should be advised complete rest, proper positioning of the affected limb and passive range of movement at the joints. Massage and intramuscular injection should be avoided during acute phase of illness. The child should be made to lie on firm bed and maintain limbs in neutral position. The child should lie with trunk and hip straight with slight flexion (5–10°) at knees and feet at right angle at ankle joint. This position can be maintained with pillows, rolled towels

or sand bags. The support should also be given on lateral sides of limb/limbs to prevent external rotation. Warm moist fomentations and passive range of movements of all the joints of affected limb/limbs should be given. As the acute phase of illness subsides, recovery in muscle power is helped by giving physiotherapy in the form of active exercises aimed at strengthening weak muscle groups, improvement of functional skills of the child, helping ambulation and prevention of deformities. Physiotherapy plays an important role in management of children during recovery and postpolio residual paralysis stage. Some children with fixed deformities and contractures may require orthopedic surgery.

PREVENTION OF POLIOMYELITIS

Two effective polio vaccines, the inactivated poliovirus vaccine (IPV), which was the first vaccine to become available in 1955, and the live attenuated OPV, licensed in 1959 are available for preventing the disease.

Oral polio vaccine induces both circulating antibody and intestinal immunity, and by secondary spread, probably protects susceptible contacts. The seroconversion after three doses of OPV has been reported to be more than 95% in developed countries but data from developing countries has shown wide variation in seroconversion and protective efficacy with rates varying from 70% against type 1 and 3 and approximately 90% for type 2 strain. OPV is most often formulated as a trivalent vaccine, containing antigens for all three poliovirus serotypes (1, 2 and 3). Trivalent vaccine is used for routine immunization of infants as well as most of the pulse polio immunization rounds. OPV is also available as a monovalent vaccine (mOPV) and bivalent (P1, P3), and has been used in specific areas where surveillance showed ongoing P1 and P3 wild virus transmission. OPV should be administered directly into the mouth. Each single dose consists of two drops. OPV is given at birth followed by three more doses at 6, 10 and 14 weeks and at 16–18 months. In addition, OPV doses are recommended as per pulse polio recommendations from time to time. OPV is one of the most heat-sensitive vaccines in common use. The vaccine should be stored at 2–8°C at all times. Unopened vials of OPV may be stored for up to 6 months at –20°C. The potency is monitored with color changes in vaccine vial monitor.

Inactivated polio vaccine Also known as Salk vaccine, IPV is a mixture of the three polioviruses made by harvesting cell culture supernatants and submitting them to inactivation by formalin. When used as primary vaccination of infants, the vaccine produces seroconversion in 90–95% of children. IPV is relatively heat stable. Risk of vaccine-associated paralysis is nonexistent with IPV and can be safely used in immunocompromised individuals.

Strategy for Polio Eradication

In May 1988, the World Health Assembly committed the member nations of the WHO to achieving the goal of global eradication of

poliomyelitis. Since most of the countries in the world are now declared as polio free, the end game strategy has been defined now by the WHO strategic advisory board on polio eradication as complete eradication and containment of all wild, vaccine and Sabin poliovirus from the world.

End Game

Trivalent OPV shall be discontinued by 2015/2016 and there will be switch to bivalent OPV. Six months before this switch, every child should receive at least one dose of inactivated polio vaccine dose with third dose of DPT at 14 weeks of age in all countries of the world who are using OPV. This strategy shall prevent circulating VDPV by augmenting the immunity induced by earlier doses of trivalent OPV. By 2019 there shall be complete cessation of OPV and at least one dose of IPV will be given to each child till 2024.

IN A NUTSHELL

1. Poliomyelitis is an important public health problem which cripples the individual. The wild virus disease is now endemic in only three countries of the world.
2. Vaccine-associated paralytic poliomyelitis (VAPP) and VDPV are the two major threats in the ultimate eradication of poliomyelitis.
3. Paralytic poliomyelitis presents as AFP (acute flaccid paralysis) which is asymmetrical in nature.
4. The important differential diagnosis of poliomyelitis includes Guillain-Barre syndrome, transverse myelitis and traumatic neuritis.
5. There are two excellent vaccines available for prevention of poliomyelitis and intelligent use of both these vaccines has led to almost eradication of this once considered dreaded disease.

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Chapter 31.3

Measles

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Measles (*Morbilli*, English Measles or *Rubeola*) is a highly contagious viral infection of the childhood. Though measles vaccination resulted in a 78% drop in measles deaths between 2000 and 2012 worldwide, the disease is still a significant cause of morbidity and mortality amongst children of developing countries. It is the leading cause of death among vaccine-preventable diseases, mainly attacking the undernourished children. Uncomplicated illness lasts for 7–10 days conferring lifelong immunity.

EPIDEMIOLOGY

Measles mainly affect children under 2 years of age, especially in developing nations with more than 80% of cases occurring in under-fives. Both sexes are equally affected; however, complication rates are higher in males. WHO estimated 122,000 measles deaths globally in 2012, i.e., amounting to almost 14 deaths every hour. These deaths represent 50–60% of deaths due to all vaccine preventable diseases. The disease burden is high in India due to poor coverage under routine immunization (48.4%, NFHS-3), and nonavailability of a second opportunity for measles vaccination in many of the states. It is estimated that more than 100,000 children die due to measles in India every year. The majority of the deaths occur in areas with poor vaccine coverage.

AGENT

Measles virus is a single stranded RNA virus belonging to genus *Morbillivirus* under family Paramyxoviridae. The virus is composed of an outer envelope and internal helical nucleocapsid. Envelope contains proteins F, H and M, and has spikes on its surface. Hemagglutinin (H) and fusion (F) proteins are important as antibodies against these two help in body's defense. The virus is rapidly inactivated by heat and ultraviolet rays. Man is the only natural host and source of measles virus. Carrier state does not exist.

TRANSMISSION

Measles spreads from the infected person to a normal individual by the respiratory route or conjunctivae via large droplets or small droplet aerosols. Sometimes large droplets or direct person-to-person contact may also spread the disease. The virus can stay suspended in atmosphere for 1 hour, hence face to face contact with the case is not necessary for the disease to occur. Period of infectivity is usually 4 days before and 5 days after the onset of rash. Immunocompromised hosts tend to remain infective throughout the illness. As measles virus is highly contagious, a 5% susceptible population is sufficient to sustain periodic outbreaks in otherwise highly vaccinated populations. More than 90% of the exposed susceptible contacts manifest the disease indicating a high infectivity.

IMMUNITY

Measles natural infection confers lifelong immunity. Serum antibodies to viral hemagglutinin, hemolysin, and complement are observed following an infection. Hemagglutinin inhibiting and neutralizing antibodies appear after 2 weeks, peak at 4–6 weeks, and decrease over a year, but persist lifelong. Children with defective cell-mediated responses are more prone to die from progressive measles infection. Acute measles results in a temporary

defect in neutrophil motility. T, B, and null lymphocytes are reduced. Interferon response appears after 10 days and coincides with recovery from acute infection. Transplacentally-acquired antibodies protect the infant for first 6–8 months of life and tend to hamper the response to live-attenuated measles vaccine given before the age of 9 months.

PATHOGENESIS

Aerosols carrying the virus enter and infect the respiratory tract where virus multiplies in tracheal and bronchial epithelial cells. This results in primary viremia (day 2–3) that infects local lymphatic tissues, perhaps carried by pulmonary macrophages. Following the amplification of measles virus in regional lymph nodes, a predominantly cell-associated viremia disseminates the virus to various organs by secondary viremia (day 5–7) resulting in systemic symptoms prior to the appearance of rash. Two types of giant cells are seen in measles: Warthin-Finkeldey cells of reticuloendothelial system and epithelial giant cells of respiratory and other epithelia. In individuals with deficiencies in cellular immunity, the virus causes progressive and often fatal-giant cell pneumonia. In immune-competent subjects, although the measles virus is cleared by virus-specific immune response, the general immune response to other antigens is suppressed. This immune-suppression is marked by decrease in delayed-type hypersensitivity, interleukin-12 production, and antigen-specific lymphoproliferative responses that persist for weeks to months after the acute infection. Immunosuppression may predispose individuals to severe bacterial infection, particularly bronchopneumonia, a major cause of measles-related mortality among younger children.

CLINICAL FEATURES

The *incubation period* from exposure to onset of symptoms ranges from 8 days to 12 days. The *prodromal phase* is characterized by fever, cough, coryza, rhinitis, conjunctivitis, malaise, and anorexia. Fever is moderate grade, continuous, and persists for at least 1 week. The *enanthematous phase* is characterized by Koplik spots on the buccal mucosa which appear on second or third day of fever. These appear as bluish-gray specks or *grains of sand* on a red base at the level of premolars. They may also occur on lips, palate, conjunctivae, gums, and vagina. In 1–2 days Koplik spots start fading or sloughing and the exanthematous rash begins to appear around fourth day of illness marking the onset of *exanthematous phase*. The rash starts from the face and neck, near the hairline; it then proceeds to the trunk, extremities, palms, and soles and lasts for about 5 days. Patients appear most ill during the first or second day of the rash and then the symptoms begin to subside. The rash is erythematous and maculopapular (**Fig. 1**). It blanches on pressure during the initial 2–3 days. Later it begins to coalesce especially on face and trunk. In later stage, the rash does not blanch and starts darkening. Generalized lymphadenopathy, mild hepatomegaly, and appendicitis may occur because of generalized involvement of lymphoid tissue. After 5 days, the *recovery phase* starts and the rash starts disappearing in the sequence in which it had appeared, leaving behind desquamated areas that spare the palms and soles (**Fig. 2**).

The typical rash may be absent in patients with underlying deficiencies in cellular immunity. Children with partial immunity develop a *modified measles* that is a milder illness with less severe symptoms and shorter duration of fever and rash. These patients do not shed virus and hence do not transmit infection to their contacts. *Hemorrhagic measles* is a severe form characterized by generalized bleeding, altered sensorium, convulsions, coma, and a high fatality rate.



Figure 1 Maculopapular rash of measles
Source: Public Health Image Library (PHIL), CDC, USA.



Figure 2 Convalescent stage of measles: desquamating rash
Source: Dr Arun Shah, Muzaffarpur, Bihar, India.

COMPLICATIONS

As discussed, measles virus weakens the immune system resulting in complications that may involve virtually any of the organ system. Complications occur in almost 30% cases of measles and are responsible for the large amount of morbidity and mortality caused this infection. Malnutrition, younger age, lack of breastfeeding, underlying malignancy or immunodeficiency, and low serum retinol (vitamin A) levels predispose to a more severe and complicated disease course.

Respiratory system complications include otitis media, sinusitis, mastoiditis, retropharyngeal abscess, tracheitis, laryngo-tracheobronchitis (croup) and bronchopneumonia. Primary tuberculosis is known to flare up following measles. Pneumonia is the most common complication in Indian context, whereas otitis media is most common in western countries. Pneumonia may be caused either by the measles virus itself or because of superimposed bacterial infection by *Staphylococcus aureus*,

Streptococcus pneumoniae, *Haemophilus influenzae*, or gram-negative bacilli including *Klebsiella*, *E. coli*, and *Pseudomonas*.

The common digestive system complications include vomiting, diarrhea, and dysentery. Giant cell formation in the gastrointestinal epithelium causes diarrhea that often gets prolonged as persistent diarrhea in poorly nourished children, hence precipitating severe acute malnutrition. Appendicitis is known to occur secondary to luminal lymphoid hyperplasia. Rare complications include hepatitis and ileocolitis.

Clinically inapparent cerebral dysfunction is observed in almost 50% of cases with uncomplicated measles in the form of electroencephalographic abnormalities and cerebrospinal fluid (CSF) pleocytosis. The most common clinically apparent central nervous system (CNS) complication is acute postinfectious measles encephalitis (APME) that occurs in approximately 0.1% of cases and leads to mortality in approximately 20% of the affected subjects. It is considered to result indirectly from the virus-induced pathogenic immune response as measles virus is generally not detected in the CNS. The onset occurs in the first week of illness. Approximately one-third develop long-term sequel. Two rare but inevitably fatal CNS complications of measles are subacute sclerosing panencephalitis (SSPE) and measles inclusion body encephalitis (MIBE). Both of these complications arise after clinically silent duration of months to years after acute infection. In contrast to APME, measles virus is abundantly detected in the CNS of subjects SSPE and MIBE. Whereas SSPE develops in fully immunocompetent individuals, MIBE is generally observed in immunocompromised patients.

Subacute sclerosing panencephalitis is a rare degenerative disease of CNS that results due to persistence of measles virus infection acquired earlier in life. It occurs with a rate of 4–11 cases of SSPE per 100,000 cases of measles. The incidence is higher in children who acquired the disease at an early age. Generally the disease process manifests 7–10 years after measles infection, but cases have been reported to occur as early as 1 month to up to 27 years after the primary infection. Pathogenesis of SSPE involves an altered measles virus lacking one of the structural proteins enabling the virus to perpetuate within the CNS cells. Higher incidence of the disease amongst subjects who acquired the disease at an earlier age suggests role of an aberrant or immature immune system as well in disease causation. The disease is characterized by gradually progressive behavioral changes like irritability, reduced attention span and temper tantrums. Poor school performance due to intellectual deterioration is a common symptom. These subtle symptoms may not provide a clue toward diagnosis but the next stage characterized by involuntary movements and myoclonic jerks in presence of maintained sensorium should prompt the clinician to consider SSPE. In late stages extrapyramidal symptoms like choreoathetosis, immobility, dystonia and rigidity appear as a result of progressive degeneration of the basal ganglia. Following this the sensorium starts deteriorating leading to dementia, stupor, coma, and finally death ensues as the vital centers located in the brainstem get involved. The stages of progression of the disease may vary among subjects. At times cognitive decline may continue for many years before manifesting the severe neuromuscular symptoms leading to delay in diagnosis. SSPE is diagnosed on the basis of the typical clinical features and at least one of the following laboratory findings, *viz.* presence of periodic complexes in electroencephalogram, elevated anti-measles IgG in CSF and serum, or isolation of virus or viral antigens from brain tissue. Postmortem diagnosis may also be established by demonstration of typical histological features in brain biopsy specimen. The sequence analysis of viral isolates from SSPE patients has shown that the disease is caused only by wild virus and never by vaccine virus. SSPE should always be suspected as a differential diagnosis

in presence of the above mentioned clinical features even if there is no definite past history of measles infection as the patient might have had an ill-defined or mild infection either due to passively acquired maternal antibodies or due to immunization. There is no definitive cure for SSPE although many drugs like amantadine, inosiplex (isoprinosine), and intraventricular interferon- μ (IFN- μ) have been tried with conflicting results. The average survival is 1–2 years since the onset of symptoms. Spontaneous remission has been reported in very few cases. The incidence of SSPE has decreased in nations with good measles vaccination coverage.

Other less commonly reported complications of measles include myocarditis, Stevens Johnson syndrome, bacteremia, cellulites, acute glomerulonephritis, and consumption coagulopathy.

Mortality from measles is often the result of complications that follow the derangement in immune system and respiratory mucosa. The leading cause of death from measles is pneumonia. Case-fatality rate is highest in under-five children.

APPROACH TO DIAGNOSIS

The clinical case definition of measles includes generalized maculopapular rash lasting more than or equal to 3 days; temperature of more than or equal to 38.3°C (101°F); and presence of cough, coryza, or conjunctivitis. Koplik spots, if present, are pathognomonic of measles. However, they are present in 50–70% children only. Inapparent or modified measles might pose a diagnostic challenge. Laboratory confirmation of the disease is not required in regions where the disease is common. In countries with good measles vaccine coverage and low prevalence of the disease, diagnosis may be confirmed by serology; viral isolation from blood, urine or respiratory secretions, or by PCR. Serum IgM becomes positive after 2–3 days after the onset of rash and persists for next 4–5 weeks. In case the sample is collected within first 3 days of onset of rash, demonstration of a fourfold rise in IgG in convalescent sera, i.e., after 2–3 weeks will confirm the diagnosis. Viral culture and molecular diagnosis by PCR are generally utilized for research purpose.

The total lymphocyte count is reduced with a greater reduction in lymphocytes as compared to neutrophils during the illness. Acute phase reactants like erythrocyte sedimentation rate and C-reactive protein are generally not altered. A rise in these would point toward presence of a superadded bacterial infection.

DIFFERENTIAL DIAGNOSIS

The differential diagnoses of fever with maculopapular rash include rubella, infectious mononucleosis, roseola, fifth disease, group A streptococcal infection, meningococemia, dengue fever, rickettsial infections, mycoplasma infections, Kawasaki disease, and drug eruptions.

Rubella is a milder disease with a characteristic postoccipital lymphadenopathy. Infectious mononucleosis should be suspected if there is generalized lymphadenopathy and hepatosplenomegaly. Children with dengue fever have a rash that is confluent and also involves palms and soles. Meningococcal and streptococcal rash are characterized by petechiae, purpura, associated with a generalized toxic look. Rash of roseola infantum (caused by herpesvirus-6) typically starts from trunk and is associated with periorbital edema. Fifth disease caused by human parvovirus B 19 (HPV 19) is characterized by an erythematous rash on the cheeks, giving these children a typical *slapped cheek* appearance.

MANAGEMENT

Uncomplicated measles, like any other acute viral illness, generally resolves on its own within 7–10 days. Hence the treatment is mainly symptomatic and directed toward managing fever, cough,

hydration and nutrition. These children can be easily managed at home and proper hygiene must be maintained. Measles being a highly contagious infection, the patients should be advised to practice respiratory hygiene measures and should be preferably isolated from unimmunized contacts.

WHO and UNICEF recommend administration of two doses of vitamin A supplements given 24 hours apart, to all children diagnosed with measles, in communities where measles-related mortality is more than 1%. There is evidence that administration of vitamin A not only reduces ophthalmic complications but it also decreases the severity of other complications as well as mortality due to measles by 50%.

Secondary bacterial infections are managed with appropriate antibiotics. Patients with complicated measles require hospitalization and should be managed accordingly.

PREVENTION

Measles vaccine is a live attenuated vaccine available in India as a monovalent vaccine as well as in combination with mumps and rubella as measles, mumps and rubella (MMR) vaccine with both the preparations having equal efficacy. The vaccine is available in lyophilized form. The reconstituted vaccine is administered subcutaneously in the upper arm or anterolateral aspect of thigh in a dose of 0.5 mL. It may be given intramuscularly as well. Its shelf-life is at least 1 year at 4–8°C. The most popular strains of measles vaccine-viruses, namely *Schwarz*, *Moraten* and *Edmonston-Zagreb* (EZ) were derived by further attenuation from the *Edmonston B* strain, which itself was attenuated from the *Edmonston A* strain. In India, Serum Institute, Pune uses EZ strain cultured in human diploid cells to manufacture the vaccine. The minimum recommended potency is 1,000 median cell culture infectious doses (CCID₅₀) of virus. Diluents must not be frozen. One hour after reconstitution, its potency drops by 50% at 20°C and if kept at 37°C almost all potency is lost. Moreover, several cases of staphylococcal toxic shock syndrome with high mortality have occurred in India after giving reconstituted measles vaccine stored for 1 or more days. Hence it must be stored at 4–8°C after reconstitution and discarded after 4 hours.

Transplacentally-acquired maternal antibodies protect not only the infants against the disease but also neutralize the immunogenic property of the vaccine if administered during infancy. Hence it should be administered at an age when majority of infants would have lost these antibodies and are susceptible to develop the disease. Therefore, in developing countries the recommended minimum age is 9 months when almost 85–95% of those vaccinated get seroconverted.

Depending upon the strain of vaccine virus, 10–20% of vaccines may develop mild to moderate fever about 6–8 days after receiving measles vaccine. It lasts for 1–3 days, and is not associated with malaise, etc. One to five percent of children may develop a few red spots on the trunk during this period.

The vaccine is contraindicated in pregnancy, significantly immunocompromised states such as leukemia, administration of antimetabolites, radiations or corticosteroids, and recent administration of immune-globulin within last 3 months. Asymptomatic HIV infection is *not* a contraindication for measles vaccination because of risk of severe life threatening measles in children with HIV infection. Hypersensitivity to eggs and neomycin is a contraindication for vaccine prepared from chick embryo cells but not for the one prepared from human diploid cell cultures.

In case of an outbreak, post-exposure immunization with live measles vaccine within 72 hours of exposure to a case may modify the illness and provide protection in certain cases. Thus, in school-based outbreaks, this may be used as a strategy for control.

Passive immunization with measles immunoglobulin within 6 days of exposure in a susceptible contact may also prevent or modify the disease. The dose is 0.25–0.5 mL/kg body weight up to a maximum of 15 mL and is given intramuscularly. It is indicated for children less than 1 year, pregnant and immunocompromised subjects who are more likely to develop complications of the disease. The vaccine must be administered at least 3 months after passive immunization. It is not recommended for controlling measles outbreak.

The EZ strain is being developed as an aerosol vaccine to immunize infants as young as 4–6 months, against measles. By utilizing the respiratory route, it is hoped to avoid neutralization by any maternal IgG antibodies that may be present.

MEASLES CONTROL STRATEGY

Routine measles vaccination coverage has been selected as an indicator of progress toward achieving MDG 4 due to the facts that measles vaccination has the potential to reduce child mortality as well as that measles vaccination coverage can be considered a marker of access to child health services. Surveys have demonstrated that the overall coverage for measles vaccine given between 9 months and 12 months is around 70%. Considering the vaccine efficacy to be around 85% for vaccination at 9 months, only around 60% ($70\% \times 85\% = 60\%$) of annual birth cohorts is actually protected against the disease leaving the rest 40% to be susceptible to measles. The second opportunity for immunization represents another opportunity for immunization for children who missed the first dose in the routine program and for children who failed to develop immunity after their first dose. Thus it is recommended by WHO and UNICEF to administer two doses of measles containing vaccine to ensure adequate protection against the disease. Routine measles vaccination for children combined with mass immunization campaigns in countries with high case and death rates are key public health strategies to reduce global measles deaths.

National Technical Advisory Group of the Government of India has recommended strengthening the coverage of routine measles immunization at 9–12 months of age; reducing the drop outs; vaccination of children at the earliest up to 5 years, who have missed the 9–12 months schedule and reporting children vaccinated over 1 year. The Group has also laid stress on skillful and standardized management of measles outbreaks.

Measles can be eradicated because man is the only reservoir of the virus; the disease occurs due to only one serotype and an effective vaccine is available.

MORE ON THIS TOPIC

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IN A NUTSHELL

1. Measles is a highly contagious acute viral illness that generally lasts for 7–10 days and confers lifelong immunity.
2. Measles is the leading cause of death amongst all the vaccine-preventable diseases. The disease burden is high in India due to poor coverage under routine immunization and nonavailability of a second opportunity for measles vaccination in many of the states.
3. The virus spreads by the respiratory route or conjunctivae. Period of infectivity is usually 4 days before and 5 days after the onset of rash.
4. The incubation period ranges from 8 days to 12 days. The illness starts with the prodromal phase followed by enanthematous, exanthematous and recovery phases.
5. Malnutrition, younger age, lack of breastfeeding, underlying malignancy or immunodeficiency, and low serum retinol (vitamin A) levels predispose to a more severe and complicated disease course.
6. The clinical case definition of measles includes generalized maculopapular rash lasting more than or equal to 3 days; temperature of more than or equal to 38.3°C (101°F) and presence of cough, coryza, or conjunctivitis. Koplik spots, if present, are pathognomonic of measles.
7. The differential diagnoses of fever with maculopapular rash include rubella, infectious mononucleosis, roseola, fifth disease, group A streptococcal infection, meningococemia, dengue fever, rickettsial infections, mycoplasma infections, Kawasaki disease and drug eruptions.
8. Uncomplicated measles, like any other acute viral illness, generally resolves on its own within 7–10 days. Hence the treatment is mainly symptomatic and directed toward managing fever, cough, hydration and nutrition. Administration of two doses of vitamin A supplements given 24 hours apart, to all children diagnosed with measles has been shown to reduce mortality.
9. Complications of measles can affect respiratory, gastrointestinal and CNS. SSPE is an inevitably fatal late CNS complication of measles.
10. Effective and safe live attenuated measles vaccine is available in India as monovalent vaccine as well as part of MMR vaccine. WHO and UNICEF recommend administration of two doses of measles containing vaccine to ensure adequate protection against the disease.

Chapter 31.4

Mumps

Shilpa Khanna Arora, Piyush Gupta

Mumps is a self-limiting, acute viral illness involving parotid and other salivary glands. It is characterized by fever, and bilateral tender swelling of salivary glands. Natural infection with mumps virus confers lifelong protection. The disease is vaccine preventable and the incidence has markedly declined in populations receiving mumps vaccine as part of routine immunization.

EPIDEMIOLOGY

The estimated incidence of mumps is around 300 per 100,000 population with majority of cases being unreported due to relatively uneventful nature of the illness. The incidence peaks during winter and spring season. Cyclic epidemic peaks are observed every 2–5 years in poorly immunized populations.

The disease occurs predominantly in children between 5 years and 15 years. Countries like USA after having introduced one dose of mumps containing vaccine in the national schedule, observed an epidemiological shift in the age group of the affected patients with more epidemics occurring in adolescents and young adults. This was attributed to waning of the vaccine-induced immune response which is considered weaker than the naturally acquired one. Inclusion of two doses of mumps containing vaccine in their national schedule has led to drastic decline in the number of cases of mumps. Mumps produces more severe disease in adults. The disease is not generally seen in infants due to the presence of transplacentally-acquired antibodies. There is no sex predilection for parotitis but CNS complications are more frequent in males. Mumps infection during first trimester increases the risk of abortion. Though the virus is known to cross placenta, it is not known to cause any congenital malformations in the fetus.

AGENT

The disease is caused by mumps virus (genus *Rubulavirus*; family Paramyxoviridae). It is a single stranded RNA virus having a lipoprotein capsule that contains some structural proteins including hemagglutinin, neuraminidase and fusion proteins that aid in viral entry within the host cells. The virus can be obtained from the saliva swab of the infected patients 7 days before and 8 days after the onset of salivary gland swelling that corresponds to the period of infectivity. The period in which a person is maximally infective is generally 2 days before till 5 days after the onset of parotid gland swelling. There is only one serotype of the virus. Humans are the only known hosts for the virus. Subclinical cases are very common and these may transmit the infection to susceptible persons. Carrier state does not exist.

PATHOGENESIS

Virus is transmitted through saliva or by respiratory droplets. The virus may also be found in urine and cerebrospinal fluid. The virus enters human body through the inhalational route and seeds the epithelium of upper respiratory tract, where it replicates. Absorption of virus in host cell is facilitated by hemagglutinin-neuraminidase (HN) surface glycoprotein, while F (fusion) glycoprotein mediates viral penetration into the cell. This is followed by regional lymphoid invasion and viremia. Mumps virus selectively targets the salivary glands, central nervous system, pancreas, testes, heart, liver, kidneys, thyroid, and joints. The virus evokes a lymphocytic response in infected tissue, with ultimate

necrosis of the salivary epithelium. Mumps virus enters the central nervous system via the choroid plexus. Cerebrospinal fluid is also characterized by a lymphocytic response. Focal ischemic infarcts are observed in the testis.

CLINICAL FEATURES

The disease can vary from a mild upper respiratory illness to viremia with widespread systemic involvement. Incubation period is generally 16–18 days but it may vary from 12 days to 25 days. The prodromal phase lasts for 1–2 days during which the child has mild to moderate grade fever, malaise, headache, vomiting, nausea and impaired appetite. The most common clinical presentation of the illness is parotitis that occurs in 30–40% of affected children. Other reported sites of infection are the testes, pancreas, eyes, ovaries, central nervous system, joints, and kidneys. The infection may remain asymptomatic in 20–30% of cases.

Parotitis is the hallmark presenting feature of mumps that is characterized by enlargement of one of the parotid glands to begin with and becomes bilateral in majority of the cases within 72 hours. Swelling of parotid is preceded by pain near the ear lobe and also difficulty in swallowing and chewing. Swelling results in obliteration of the angle of the jaw and lifting of the ipsilateral ear lobe, upward and outward. The swelling increases in size for 3–4 days. Disease may remain unilateral in 30% cases. In 10% of cases there occurs inflammation and swelling of other salivary glands as well. Lymphatic obstruction in facial and neck planes may result in local edema, extending up to sternum.

Recovery begins as fever begins to subside in 3–5 days. Parotid swelling starts receding after 5 days. It may take 10–14 days for the swelling to subside completely.

COMPLICATIONS

Neurological manifestations are the most common extrasalivary manifestation of mumps infection. The frequency with which mumps virus infects the nervous system is quite high to the extent that it is regarded as a neurotropic virus by many researchers. The CNS affliction of mumps virus may range from relatively benign aseptic meningitis in majority of the cases to severe meningoencephalitis in a small number of cases. The neurological complications are seen more often in males as compared to females (ratio 3:1 to 4:1). Asymptomatic pleocytosis in CSF is seen to occur in almost 50% of all children with mumps but the incidence of symptomatic disease is around 10–15% of the cases.

Aseptic meningitis is the most common complication with an incidence of around 10% of all the cases of mumps. It is manifested as severe headache, photophobia, and neck stiffness due to spasm of the spinal muscles. It appears within a few days of parotid swelling and generally resolves in 7 days without any complication. Mumps meningitis may also occur in absence of any parotid swelling. Death due to mumps is exceedingly rare, and is mostly caused by mumps encephalitis. Encephalitis occurs in 0.1% of the cases which is much less than meningitis and is characterized by seizures, altered sensorium or focal neurological deficits. It may manifest before, with, or after the appearance of parotid swelling. *Early onset encephalitis* occurs within 1–2 weeks of onset of swelling and is due to mumps infection of the brain. *Late onset encephalitis* is an immune-mediated demyelinating condition. Some cases experience ataxia, behavioral changes, and abnormalities in electroencephalography during convalescence, but they also resolve after a few weeks. Mortality occurs in about 1.5% of the cases. Long-term morbidities like permanent unilateral sensorineural hearing loss are not very common (0.005%).

Other neurological manifestations of mumps include cerebellar ataxia, acute disseminated encephalomyelitis, aqueductal stenosis,

facial nerve involvement, auditory nerve involvement leading to permanent hearing deficit, transverse myelitis, and Guillain-Barré syndrome. Although most patients recover without prolonged sequel, the mortality rate is reported to be up to 1.4%.

Epididymo-orchitis occurs in about 30% of postpubertal adolescents with mumps but is rare in prepubertal males. It is bilateral in less than one-third of the cases. Although testicular atrophy is known to occur, sterility is rare. In postpubertal adolescent girls, mastitis and oophoritis can occur. Pancreatitis is seen in about 4% of patients with mumps and may occur even in absence of parotitis. There is evidence suggesting that mumps virus infection of the pancreatic beta cells may trigger the onset of insulin-dependent diabetes mellitus. Additional rare complications include glomerulonephritis, arthritis, myocarditis, endocardial fibroelastosis, thrombocytopenic purpura, mastitis, thyroiditis and keratouveitis.

APPROACH TO DIAGNOSIS

In populations having a high prevalence of mumps, it is diagnosed on the basis of the typical clinical presentation as described above. History of exposure to a case of mumps 2–3 weeks back would support the diagnosis. Laboratory confirmation of parotitis can be made on the basis of elevated serum amylase levels. Presence of leukopenia with relative lymphocytosis indicates a viral etiology. CNS infections exhibit a lymphocytic pleocytosis in cerebrospinal fluid, with hypoglycorrhachia.

The diagnosis of mumps in populations with low disease prevalence can be difficult and require viral isolation or detection of mumps virus nucleic acid by reverse transcriptase-polymerase chain reaction. This may be carried out in specimens from exudates of Stensen's duct using buccal swabs, nasopharyngeal swabs, throat washings, saliva, urine, blood, or cerebrospinal fluid. Though the mumps virus can be isolated from 7 days before up until 9 days after the onset of parotitis, the yield is highest only during the first few days of the illness in highly immunized populations. Thus clinical specimens must be obtained within 1–3 days after the onset of parotitis. Serological diagnosis can be made by detection of mumps-specific IgM antibody, or by a significant increase between acute and convalescent titers in serum mumps IgG antibody by complement fixation, hemagglutination inhibition, or enzyme immunoassay. Serological confirmation in highly immunized populations may be challenging as the IgM response may be absent or short lived; and acute IgG titers already might be high, so no significant increase can be detected between acute and convalescent specimens. Hence, a negative IgM in an immunized child does not exclude the diagnosis.

DIFFERENTIAL DIAGNOSIS

Parotitis characteristically results in obliteration of the angle of the jaw and lifting of the ipsilateral ear lobe in an upward and outward direction. At times one may need to differentiate it from an enlarged cervical lymph node. For this, draw an imaginary line bisecting the long axis of the ear to the angle of jaw. A cervical lymph node usually lies posterior to this imaginary line, while a parotid swelling overlies this line.

Differential diagnoses of a parotid swelling include suppurative parotitis caused by gram-positive bacteria like *Staphylococcus aureus*, gram-negative bacteria and nontuberculous mycobacteria. Suppurative parotitis is usually unilateral, extremely painful and may be accompanied by purulent discharge from Stensen's duct. Parotitis can also be caused by other viruses including parainfluenza types 1 and 3, influenza A virus, HIV, Epstein-Barr virus, enterovirus and cytomegalovirus. Mumps virus is the only known cause of epidemic parotitis. Noninfective parotitis is caused

by collagen vascular disorders (systemic lupus erythematosus, Sjögren syndrome), malignancies (leukemia, lymphoma), and obstruction of salivary gland duct due to calculus.

MANAGEMENT

Majority of the cases of mumps resolve spontaneously within 2 weeks without any significant complications or sequel. Thus the management is mainly supportive with the use of paracetamol for fever. Patients are advised to avoid sour food and drinks as they irritate the already inflamed salivary glands. Hot or cold packs may be applied locally under supervision to reduce inflammation. Warm salt water gargles, soft foods, and extra fluids may also help relieve symptoms. Sucking on lozenges that stimulate the salivary secretions helps in reducing the swelling. There is no specific antiviral therapy against mumps. Uncomplicated cases may be managed on outpatient basis. Patients should preferably be isolated and advised to follow droplet precautions for at least 5 days from the onset of parotitis.

Complications should be treated based on the presentation. For orchitis, testicular ultrasonography should be obtained; ice-packs must be applied locally to reduce swelling along with scrotal support. Anti-inflammatory agents might help in faster recovery of orchitis. Pancreatitis is managed by intravenous hydration and rigorous monitoring. Meningitis or encephalitis is managed symptomatically.

PREVENTION

Care of Contacts

Affected children should preferably be isolated and not allowed to go to school for 7–10 days after the onset of parotid swelling. Unlike measles, postexposure prophylaxis is not effective with mumps vaccine and there is no role of mumps immune globulin. Measles, mumps, and rubella (MMR) vaccine can be given after exposure to provide protection against future exposures and confer immunity against other two antigens. Immunization during the incubation period of the disease does not increase the risk of any complications.

Active Immunization

Mumps vaccine is a live attenuated vaccine and is available in India as part of the combined MMR vaccine. The minimum recommended potency is 1,000 median cell culture infectious doses (CCID₅₀) of virus. The shelf-life of the lyophilized vaccine is 1 year at 4–8°C. The reconstituted vaccine can be administered subcutaneously or intramuscularly in a dose of 0.5 mL. Once reconstituted, it should not be used after 4 hours. Most commonly, the vaccine consists of the Jeryl-Lynn strain. Other strains in use are Leningrad-3 (erstwhile Soviet states); Urabe (Japan, France, Italy), L-Zagreb (Croatia, India, Slovenia), and Rubini (Switzerland). The ideal age for vaccinating children is 15–18 months. The vaccine is administered in a dose of 0.5 mL subcutaneously. MMR can be given to individuals who are already immune to one or more component viruses of the vaccine.

The antibody levels induced by the vaccine are generally lower and less long lasting as compared to that following natural infection. The immunogenicity of the vaccine depends on the virus strain used with the majority of them resulting in seroprotection in more than 80% of the vaccine recipients. The antibody levels tend to fall with time; hence a second dose of mumps containing vaccine is being administered in many of the developed nations of the world and is being considered in regions with good vaccination coverage in order to avoid epidemic resurgence of the disease.

Adverse events to mumps vaccine are rare. Aseptic meningitis is reported in 0.1–100 per 100,000 vaccines. The vaccine is

contraindicated in pregnancy, history of anaphylactic reaction to egg, presence of immunodeficiency disorders, those receiving immunosuppressive drugs, and persons who have received immunoglobulins or blood transfusion recently in the past 3 months. For such patients, who cannot be vaccinated, it is advisable to vaccinate their close susceptible contacts (cocooning). Vaccine-virus is not transmitted by immunized persons.

MUMPS CONTROL STRATEGY

By the year 2000, approximately 120 countries or regions had included vaccination against mumps in their national immunization programs, mostly as MMR vaccine. Most countries in Africa and South-East Asia Region have not adopted this strategy and the incidence of mumps remains high in these territories. Only few states in India have incorporated MMR in their routine immunization schedule in a single dose between 15 months and 18 months of age.

Mumps infection can be controlled through high (more than 90%) routine coverage with MMR vaccine administered at 15–18 months of age. Following the trend observed in the developed countries, with the increasing routine vaccination coverage, a shift in the epidemiological profile of these diseases to a higher age group may not be ruled out in India. To avoid this there is a need to provide a second opportunity for immunization in regions with less than 80% coverage with the first dose. The catch-up immunization of susceptible cohorts may also be achieved targeting the vulnerable age groups in order to head toward mumps elimination.

MORE ON THIS TOPIC

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IN A NUTSHELL

1. Mumps is a self-limiting, acute viral illness causing inflammation of parotid and other salivary glands.
2. The disease commonly occurs in the age group of 5–15 years. Natural infection with mumps virus confers life-long protection. The disease occurring in adults is more severe.
3. The mumps virus is transmitted through saliva or by respiratory droplets. The period of maximum infectivity is 2 days before till 5 days after the onset of parotitis.
4. The most common clinical presentation of the illness is parotitis (30–40%). The infection may be asymptomatic in 20–30% of cases.
5. Neurological manifestations are the most common extrasalivary manifestation of mumps infection. Other reported sites of infection are the testes, pancreas, eyes, ovaries, central nervous system, joints and kidneys.
6. The diagnosis is mainly clinical. History of exposure to a case of mumps would support the diagnosis.
7. The differential diagnosis of parotitis includes cervical lymphadenopathy, suppurative (bacterial) parotitis, viral parotitis and noninfective parotitis caused by collagen vascular disorders, malignancies and salivary gland calculus.
8. The management is mainly supportive. Spontaneous recovery occurs in 2 weeks in majority.
9. The disease can be prevented by administration of the mumps vaccine which is a very safe and effective vaccine and is available as a component of MMR vaccine.
10. Several countries have been able to reduce the incidence of mumps drastically after inclusion of MMR vaccine in two dose schedule in their national immunization program.

Chapter 31.5

Rubella

Pooja Dewan, Piyush Gupta

Rubella or German measles or third disease is usually a mild illness caused by the rubella virus. Rubella commonly affects children, though it can affect people of all age groups. Depending on the (acquired) age of presentation, rubella infection is categorized as *postnatal rubella infection* or *congenital rubella infection (CRI)*.

EPIDEMIOLOGY

Rubella is distributed worldwide. Man is the only host for rubella virus and there is no known animal reservoir. There is no true carrier state for rubella, though infected infants are known to shed the virus for extended periods. During the acute illness the rubella virus may be carried in the naso-opharynx, urine, stool, or cerebrospinal fluid. Rubella is contagious and transmission occurs by droplet spread and the virus multiplies in the oropharyngeal epithelium and regional lymph nodes. This is followed by a viremic phase lasting for 2 weeks. Viral shedding continues in the respiratory secretions, urine and stool. Postnatal rubella is infective from 7 days before to 14 days (median 5 days) after the appearance of rash. The maximum period of infectivity lasts from 7 days before until 7 days after the appearance of rash.

Congenital infection occurs by transplacental spread and the virus replicates extensively in the fetus. Infants with CRI can shed rubella virus in urine throughout infancy. Rubella virus can also be isolated from the lenticular aspirates during early childhood in infants with congenital rubella cataracts. Rubella infection in the fetus can lead to widespread tissue damage. The spectrum of organ damage in the infants includes the brain, heart, eyes, and auditory nerve. The exact mechanism of cellular injury is not clear, but ischemia, chromosomal breaks, and mitotic arrests could have some role.

Prior to the use of rubella vaccines, the disease occurred in epidemics affecting mainly children, occurring in 6–9-year cycles. With the introduction of rubella vaccines in 1970s and 1980s, most cases occurred in young unimmunized adults. Since then, rubella and congenital rubella syndrome (CRS) has decreased dramatically in the western hemisphere. The World Health Organization set goals for elimination of rubella and CRS in the WHO Region of the Americas by 2010 and European Region by 2015. Pan American Health Organization confirmed that the region of the Americas had achieved the rubella and CRS elimination goals in 2012. While the western hemisphere has managed success in its efforts to control CRS, most of the developing countries, including India, continue to grapple with the morbidities and long-term effects of CRS.

AGENT

Rubella virus is a single stranded RNA virus belonging to the genus *rubivirus* which belongs to the family *Togaviridae*. Humans are the only source of infection.

CLINICAL FEATURES

Postnatal/Acquired Rubella

Postnatal rubella is a mild disease similar to other viral illnesses in childhood. The incubation period for postnatally acquired rubella ranges from 14 days to 21 days, usually 16–18 days. Postnatal (or acquired) rubella infection is usually a mild febrile illness associated with rash and lymphadenopathy. Natural infection confers lifelong immunity. Most cases of postnatal rubella infection are often

subclinical. The disease in children is often milder and recovery is much faster than in adults. The usual presenting features include fever, rash, lymphadenopathy and arthralgia/arthritis.

The illness usually begins with mild febrile illness characterized by temperature of about 37.5–38.5°C. The other features commonly associated include running nose, coryza, headache, myalgia, and mild conjunctivitis. The rubella rash appears as either pink or light red spots on the face and neck, which may merge to form evenly colored patches. The rash spreads starting from face to the rest of the body. The rash can itch and lasts for 2–3 days. As the rash clears, the affected skin occasionally sheds in very fine flakes. On the first day of appearance of exanthem, small pink-colored ring lesions and petechiae also appear on the soft palate known as *Forchheimer spots* (pathognomonic of rubella infection). Tender and enlarged lymph nodes usually involving the suboccipital and postauricular group of lymph nodes, lasting 5–8 days are also seen. Lymphadenopathy may precede the rash. Polyarthralgia and polyarthritis seen in rubella is usually transient. It is rarely seen in children but is common in adolescents and adults, especially females. Other complications like thrombocytopenia, encephalitis, myocarditis and Guillain-Barré syndrome are rarely seen.

Congenital Rubella Infection

Maternal rubella infection during pregnancy can result in fetal infection by transplacental spread. Fetal rubella infection can in turn result in miscarriage, fetal death, or a spectrum of multisystem abnormalities in the infant referred to as the CRS. Teratogenic effects of maternal rubella infection can be seen in up to 90% of neonates and infants if maternal infection occurs during the first 12 weeks of gestation. This reduces to about 25% and 11%, if maternal infection occurs during the 13–14 weeks of gestation and 15–16 weeks, respectively. Maternal infection after the 16th week has a low risk for teratogenic effects in fetus. The infected infant may be symptomatic in the neonatal period (early onset disease) and develop evidence of CRS subsequently (late onset disease). **Table 1** depicts the spectrum of anomalies seen in CRS which may present early or late.

DIAGNOSIS

Rubella-specific IgM antibodies usually indicate recent postnatal infection or congenital infection in a newborn infant. Rubella antibodies (IgM) can be detected by 5th day of acquired rubella. For diagnosis of postnatally acquired rubella, a fourfold or greater increase in antibody titer or seroconversion between acute and convalescent IgG serum titers also indicates infection.

Most congenital rubella cases are IgM-positive at birth up to 3 months of age. Rising rubella-specific IgG titers in blood

Table 1 Clinical features of congenital rubella syndrome

Early onset disease	<i>Ophthalmologic:</i> Cataracts (Fig. 1), glaucoma, pigmentary retinopathy, microphthalmia <i>Cardiac:</i> Patent ductus arteriosus, pulmonary stenosis or septal defects <i>Neurological:</i> Microcephaly, behavioral disorders, meningoencephalitis, mental retardation <i>Auditory:</i> Sensorineural deafness <i>Others:</i> Hepatosplenomegaly, thrombocytopenia, dermal erythropoiesis (blue-berry muffin rash, Fig. 2), radiolucent bone disease, and intrauterine growth retardation
Late onset disease	<i>Ocular abnormalities:</i> Cataract, glaucoma, retinal detachment <i>Endocrinal disorders:</i> Diabetes mellitus, thyroid dysfunction <i>Psychomotor defects</i>



Figure 1 Cataract in a child with congenital rubella syndrome
Source: Public Health Image Library (PHIL), CDC, USA.



Figure 2 This infant presented with *blueberry muffin* skin lesions indicative of congenital rubella. Such lesions represent sites of extra-medullary hematopoiesis, and can be associated with several different congenital viral infections and hematologic diseases. The rash and fever last for 2–3 days. The illness is mild in children and young adults
Source: Public Health Image Library (PHIL), CDC, USA.

during the first 7–11 months of life also suggest CRI. Diagnosis of CRI beyond infancy is difficult and may be tried by viral cultures from tissue samples including throat and nasal specimens or lens aspirates. Detection of rubella virus RNA by reverse-transcriptase polymerase chain reaction, followed by genotyping of strains can aid epidemiology.

DIFFERENTIAL DIAGNOSIS

Several febrile illnesses with rash can present with similar clinical features and hence the diagnosis of rubella can be challenging. Conditions to be considered in the differential diagnosis of rubella are detailed in **Table 2**.

TREATMENT

Treatment of acquired rubella infection is only supportive. Acetaminophen can be given for fever.

PROGNOSIS

The prognosis for acquired rubella is generally excellent. Rubella infections usually clear within 2–3 weeks and also provide lifelong immunity against the virus. However, pregnant women infected with rubella have a spontaneous abortion rate of about 5% and a stillborn rate of 1–2%. Prognosis for the infected neonate depends on the extent of damage. Severely affected infants can have mortality rates of up to 20% in the first year of life. Mothers infected in the first month of pregnancy deliver neonates with serious permanent damage in 50% of such cases. Sequelae in early childhood include growth retardation during preschool years, microcephaly, cataracts, deafness and congenital heart disease. In teenage and early adult life thyroid disorders develop in 5% of survivors. About 20% of them develop diabetes by the third decade of life. Panencephalitis is a delayed and dreaded complication of CRS. Long-term outcomes of CRS are variable and survivors with malformations have to cope with medical, social, emotional and economic handicaps.

PREVENTION AND CONTROL

Isolation of infected individual is recommended to prevent spread of illness to others. For individuals affected with postnatal rubella, droplet precautions are recommended till up to 7 days after onset of the rash. For children with proven or suspected congenital rubella, isolation is recommended until they are at least 1 year of age, or unless two cultures of clinical specimens obtained 1 month apart after 3 months of age are negative for rubella virus.

Active Immunization

Childhood rubella is a mild clinical illness and hence does not necessitate routine prophylaxis; immunization is necessary only to prevent CRS. There are several approaches which have been used in different countries to eliminate CRS:

- Immunization of infants and young children
- Immunization of adolescent females and/or women of childbearing age
- Immunization of adolescent males and females
- Immunization of infants and adolescent girls and adult women (best approach)
- Immunization of hospital personnel.

Each of the above approaches has their own limitations which may hamper complete elimination of CRS. *Selective immunization of adolescent girls and/or women of childbearing age* alone may be inappropriate as unvaccinated girls (e.g., those who refuse vaccination) will still be exposed to circulating rubella virus in male population and children. Universal immunization of infants and young children of both sexes will reduce the circulation of virus. However, pregnant women would still continue to be exposed to rubella in adults. It is now realized that combining universal immunization of infants and children with vaccination of adolescent girls and adult women is the most effective approach to eliminate rubella and CRS.

The Vaccine

The first rubella vaccine was licensed for use in 1969. Most of the currently licensed vaccines are based on the live, attenuated RA27/3 strain of rubella virus, propagated in human diploid cells. Each dose of this vaccine contains a defined number of active virus particles (> 1,000 TCID₅₀). Other attenuated rubella vaccine strains, such as the Matsuba, DCRB 19, Takahashi, Matsuura, TO-336 and BRD-2 strains are used in Japan and China.

The rubella vaccine is usually offered as a live attenuated virus, usually given as part of combination vaccines like MMR vaccine (protecting against measles, mumps, and rubella) or

Table 2 Differential diagnosis of acquired rubella infection

Scarlet fever	Rash appears on the second day of illness characterized by fine red points on an erythematous background. The flexural surfaces may have hemorrhagic staining. Sore throat and enlargement of lymph nodes below the ear are common features. Strawberry tongue is seen. Eyes are usually not congested or watery. The rash takes several days to fade and as the rash fades a dark punctuate discoloration may be seen on shoulders or bends of elbows. Rash may be associated with peeling of skin.
Measles (rubeola)	Headache, malaise, and coryza are seen on the first day. Fever may be high grade and child may be listless and toxic. Koplik spots appear on the second day while the rash comes out late on the third day. The eyes are usually catarrhal (conjunctivitis). Tongue may be dry and furred. In measles a blotchy mottling on the parts where the rash has been is seen and it may persist for a few days after the illness and is described as postmeasles staining.
Kawasaki disease	Prolonged fever associated with constellation of clinical features like conjunctivitis, erythematous swelling of hands and feet, cervical lymphadenopathy, oropharyngeal lesions, and uveitis. Rash is polymorphous and may be localized to extensor aspects of lower limbs and groin. Coryza is usually absent.
Exanthem subitum	Rash appears on the fifth day of fever. Rash is usually discrete maculopapular starting from trunk and spreading to face and extremities. Illness is accompanied by irritability and occipital lymphadenopathy. Rash does not peel.
Erythema infectiosum	Usually no prodromal symptoms are seen. Cheeks appear red and indurated. The rash is symmetrical, maculopapular, confluent, and over the extensor face of upper and lower limbs. Rash does not peel.
Enteroviral infections	Prodromal period (usually 3–5 days) is seen. Rash is maculopapular discrete, nonitchy and generalized. Rash is not associated with peeling. Aseptic meningitis may be seen.
Infectious mononucleosis	A prolonged prodromal illness. Pleomorphic rash usually preceded by intake of ampicillin. There is associated hepatosplenomegaly, membranous tonsillitis, and lymphadenopathy. Rash is not associated with desquamation.
Drug reactions	Confluent maculopapular rash which may be seen with fever and mild constitutional symptoms. There is usually a history of drug intake prior to the appearance of symptoms.
Dengue fever	Seen in patients with a history of recent travel to an endemic region during the rainy season. It presents with an influenza-like profile with a maculopapular morbilliform or scarlatiniform rash. The illness may be complicated by bleeding and shock.

MMRV vaccine (protecting against measles, mumps, rubella and varicella) in children. The immune response to rubella antigens is not affected by the other vaccine components. It may be given as a monovalent vaccine, i.e., rubella vaccine (alone) or as bivalent MR (protecting against mumps and rubella) in adolescents and adults.

Dosage

The rubella containing vaccines (RCVs) are given either subcutaneously or intramuscularly. In children two doses of MMR vaccine are recommended; first dose at 12–15 months (not earlier as the maternal antibodies can persist up to 12 months) and the second dose when the child is 4–6 years old. A single dose of MMR administered after infancy provides adequate protection till 5 years age. However, a second dose given at 4–6 years offers 95–100% protection. All older children (≤ 12 years) should receive at least one dose of rubella vaccine. Vaccine-induced immunity is generally lifelong.

Adverse Reactions

Adverse reactions to rubella vaccine include fever (5–7 days after vaccination in 5–15% of recipients), lymphadenopathy, arthritis/arthralgia of peripheral joints, and transient skin rash, all of which are self-limiting. Joint involvement usually begins 7–21 days after immunization and generally is transient. The incidence of joint manifestations after immunization is lower than that after natural infection at the corresponding age. Previously, rubella vaccine was believed to be associated with Guillain-Barré syndrome, autism, ulcerative colitis and aseptic meningitis, all of which have been now refuted.

Contraindications

Pregnancy is an absolute contraindication for rubella vaccination. Also, any woman who receives a RCV should not conceive within 28 days of receiving the vaccine (CDC). Persons receiving blood products (except washed red cells) or immunoglobulins should not receive RCV up to 3–12 months after receiving the transfusion. Immunocompromised states like those receiving cancer chemo-

therapy or high doses of steroids (2 mg/kg or greater or more than 20 mg/day) for 14 days or more are also contraindications for rubella vaccination. Persons with serious allergies to gelatin or components of vaccine should refrain from receiving RCV. Persons with HIV infection but no AIDS can receive RCV.

Postexposure Prophylaxis

If a pregnant mother is suspected of having been exposed to possible rubella during early pregnancy, a blood specimen should be obtained as soon as possible and tested for rubella antibody (IgG and IgM). An aliquot of serum should be stored for possible repeated testing at a later time. The presence of rubella-specific IgG antibody in a properly performed test at the time of exposure indicates that the person most likely is immune. If antibody is not detectable, a second blood specimen should be obtained 2–3 weeks later and tested concurrently with the first specimen. If the second test result is negative, another blood specimen should be obtained 6 weeks after the exposure and also tested concurrently with the first specimen; a negative test result in both the second and third specimens indicates that infection has not occurred, and a positive test result in the second or third specimen but not the first (seroconversion) indicates recent infection. If the infection is confirmed (mothers with IgM positive or rising IgG titers), medical termination of pregnancy may be advised.

SURVEILLANCE

Methods for surveillance of CRS include hospital record review, deaf/blind surveys, clinician reporting, and active search for cases with CRS after outbreaks of acquired rubella. Serological surveillance among antenatal women can be used to monitor the impact of the immunization program. The WHO has established a Measles-Rubella Laboratory Network (LabNet) in 2002 which comprises of a total of National Reference Laboratories supervised by Regional Reference Laboratories to enable high quality laboratory surveillance of suspected rubella and CRS cases worldwide.

IN A NUTSHELL

1. Rubella is usually a mild exanthematous illness caused by the rubella virus affecting humans worldwide.
2. Man is the only host for rubella virus and there is no known animal reservoir.
3. The illness is characterized by mild fever, rash, arthralgia, and lymphadenopathy. Fetal rubella infection due to transplacental spread from affected mothers result in miscarriage, fetal death, or a spectrum of multisystem abnormalities in the infant referred to as the CRS.
4. Congenital rubella syndrome is characterized by a triad of sensorineural deafness, ophthalmologic and cardiac abnormalities.
5. Rubella can be eliminated.
6. Active immunization of children, adolescent females, and women in reproductive age group with RCVs and active surveillance is recommended to decrease CRS burden.

MORE ON THIS TOPIC

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Chapter 31.6

Varicella

Piyush Gupta, Aashima Dabas

Varicella (chickenpox) is a highly infectious disease caused by primary infection of varicella-zoster virus (VZV). The illness is characterized by an exanthematous vesicular rash with a centripetal distribution. The rash typically begins as maculopapular lesion on first day of fever. The course is usually benign and lasts for about 7 days. Chickenpox infections give lifelong immunity. However, VZV can remain latent and activate years later as herpes zoster (shingles). Primary disease causes substantial morbidity but is vaccine preventable.

EPIDEMIOLOGY

The virus infects only primates and man is the only reservoir. All age groups can be infected with predisposition for younger ages. Since the introduction of varicella immunization in developed countries, the infection prevalence is more during later school years than preschool age. The disease usually occurs during hot temperate climate season. Immunocompromised patients, infants and adults are more prone to develop serious disease.

AGENT

Varicella-zoster virus is an enveloped DNA virus of the Herpes virus family. Three major genotypes of the virus (Japanese, European, and Mosaic) are identified, but only one serotype is known. The wild VZV and the vaccine-derived VZV can be distinguished by restriction enzyme analysis of genome. The virulence of wild-VZV is due to the glycoproteins produced during viral replication. These glycoproteins contribute to structure of virions, are antigenic, and promote adhesion and entry of VZV into uninfected cells.

TRANSMISSION

Varicella virus is transmitted from a varicella patient to others mainly by direct contact from skin lesions. In addition, the airborne route also contributes to VZV spread as VZV has been detected by polymerase chain reaction (PCR) in nasopharynx of children during pre-eruptive stages of the infection. Crusts from chickenpox lesions do not contain live virus. Infectivity is therefore maximum during prodromal period and wanes off when eruptions become crusted. Period of infectivity ranges from 48 hours prior and up to 3–7 days after the rash appears. The lesions of herpes zoster also contain infectious VZV and are contagious, though less contagious than varicella eruptions. Varicella is known to occur after exposure to a patient with zoster. Zoster, *per se*, is not acquired by contact with a patient with varicella or zoster. It occurs in states with depressed cell-mediated immunity due to reactivation of VZV multiplication in the body.

Varicella virus is transmitted to 65–86% of susceptible household contacts. This secondary attack rate is lower in a school setting. A single exposure to varicella is sufficient to result in lifelong immunity to VZV and second attacks of varicella are rare (may occur in immunocompromised). Zoster is unusual in children less than 10-year-old but may occur if chickenpox is acquired in early infancy. The lifetime risk for a person to develop zoster after history of varicella is 10–20%.

PATHOGENESIS

Airborne virus enters the oropharynx through inhalation by droplet infection. Primary seeding occurs in tonsillar tissue and mucosa of the upper respiratory tract. Virus replication for initial

10 days is followed by primary viremia that spreads the virus to reticuloendothelial system. No clinical symptoms occur during this primary low-grade viremic phase. Skin lesions appear only during the secondary viremic phase that lasts for 3–7 days. Infectious virus is carried to vesicular fluid and also back to respiratory mucosa, from where it is shed, transmitting infection to susceptible contacts. Alternately, VZV may reach the keratinocytes directly by virus-infected CD4 memory T-cells. VZV may be transported to the dorsal root of spinal cord, where a latent infection is established. Reactivation of this focus at a later stage results in herpes-zoster.

The cell-mediated immunity acts as chief defense with contribution from humoral immunity. Natural killer cells and antibody-dependent cell cytotoxicity are also implicated in defense. The cell-mediated immune reactions remain positive for many years and IgG antibody to VZV may be detectable for decades in adults after recovery. Despite presence of adequate cell-mediated and humoral immunity, few people may still develop milder clinical illness following exposure to wild VZV (*breakthrough varicella*).

The histological changes in skin are similar to both varicella and zoster with the presence of multinucleated giant cells with intranuclear inclusions in the epidermis and dermis. There is accompanying intercellular edema which separates the skin layers to result in a vesicle. In zoster, in addition to above, an inflammatory infiltrate is present in dorsal root ganglion of the affected dermatome.

CLINICAL FEATURES

Chickenpox occurs at all ages (including neonates) with peak incidence between 2 years and 8 years. The median incubation period is 14–16 days (range 10–21 days). The disease ushers in with fever and malaise. Prodromal symptoms also include headache, sore throat, and backache. Prodromal symptoms are frequent in adults but may be absent in children where rash may be the only presenting symptom. The rash appears within 24 hours of the onset of prodrome. Fever is usually moderate, usually between 38.8°C (102°F) and 39.4°C (103°F), but may rise to 41.1°C (106°F). Fever usually resolves after 3–4 days of appearance of rash.

Evolution of the Rash

The rash begins as crops of macules, which evolve into papules and then vesicles. The vesicles are initially filled with clear fluid that soon becomes cloudy. The vesicles persist for 3–4 days, become pustular and then form crust. The vesicles may be round, oval, elliptical or irregular, often surrounded by red areola. The lesions first appear over face, scalp, or trunk, and then spread to whole body. Palms and soles are spared. The lesions measure 5–10 mm in diameter. New lesions may keep occurring over 1 week. Most children have more than 250 lesions. Macules, papules, vesicles and scabs can be seen simultaneously. Lesions tend to be more abundant on covered than exposed parts of the body. By the time of vesicle formation, there is excessive itching. Vesicles may also be observed over conjunctiva, palate, tongue, and buccal mucous membranes. Vesicles dry up within 1–2 days, starting from the center, forming crusts and scabs. Scabs fall off in 10–20 days. Underlying skin becomes hypo- or hyperpigmented that stays for days to weeks. Permanent scarring is unusual.

Subclinical varicella is rare, but few adults with no prior history of disease or vaccination to VZV may show detectable antibodies to VZV.

COMPLICATIONS

Bacterial Infections

Secondary skin infection due to Group A *Streptococcus* and *Staphylococcus aureus* results in cellulitis, erysipelas, and

skin abscesses. Bacteremic spread may lead to pneumonia, osteomyelitis and septic arthritis.

Neurological Complications

Neurological complications occur towards the end of first week of illness as the rash reaches maturity. The most common manifestation is a pure cerebellar ataxia which has an excellent prognosis. Meningoencephalitis is a dreaded complication with 5–25% mortality. Acute disseminated encephalomyelitis (ADEM) is a rare form of postvaricella encephalitis with cerebral demyelination. It presents with cranial nerve involvement, long tract signs, and convulsions. Transverse myelitis, acute infantile hemiplegia, and Guillain-Barré syndrome are the other neurological complications. Chronic neurological sequels are rare.

Pneumonitis

Varicella pneumonia appears 3–5 days after the onset of rash. These children present with acute respiratory distress and hemoptysis and diffuse nodular infiltration in chest radiograph.

Others

Myocarditis, pericarditis, endocarditis, hepatitis, glomerulonephritis, appendicitis, keratoconjunctivitis, arthritis, thrombocytopenia, and purpura fulminans are the other notable complications. Immunocompromised children infected with HIV may develop chronic wart like lesions of VZV due to low grade persistent infection.

DIAGNOSIS

The diagnosis of varicella is essentially clinical. The rash of chickenpox needs to be differentiated from other causes of vesicubullous rash: (1) infections with herpes simplex, rickettsia, infected scabies, *S. aureus*; and (2) noninfecting conditions including contact dermatitis, drug reactions and insect bites. Routine laboratory investigations are not essential. Leukopenia is typical during the first 72 hours, followed by lymphocytosis. Liver enzymes may be mildly elevated.

- **Rapid laboratory diagnosis** can be made by electron microscopy or by immunofluorescence. VZV can be identified by direct fluorescence assay of cells from the vesicles or by PCR amplification testing. Presence of multinucleated giant cells on Tzanck smear is nonspecific. The virus may also be detected by PCR from the respiratory secretions or cerebrospinal fluid.
- **Virus isolation and culture methods** are successful only when done early in the disease course. Isolation of VZV is difficult from dry or crusted skin lesions. Viral culture, however, is time taking and not routinely performed.
- **IgG antibodies** to VZV can be detected by latex agglutination or enzyme-linked immunosorbent assay. A fourfold rise in antibody titer in acute and convalescent sera, or raised IgM-VZV antibody level in a single sample, is confirmatory of acute infection.

TREATMENT

Supportive Therapy

No treatment is usually required and bed rest is unnecessary except in ill children. Paracetamol usually controls prodromal symptoms and fever. Aspirin should not be given because of the risk of Reye syndrome. Calamine lotion will normally soothe pruritus; if not, an antihistaminic should be tried. If the enanthem is severe, careful oral toilet is needed. Lesions on the conjunctiva should be protected from secondary infection.

Specific Therapy

Acyclovir therapy is not recommended routinely for treatment of uncomplicated chickenpox in the otherwise healthy child because of marginal benefit, cost of the drug and low risk of complications of the disease. Oral acyclovir to healthy children within 24 hours of onset of rash decreases the duration of rash by 1 day and number of new lesions by only 25%.

Indications for acyclovir in varicella infection are as follows:

- Chronic cutaneous or pulmonary disorders
- Those receiving short-term, intermittent or aerosolized corticosteroids
- Those receiving long-term salicylate therapy
- Immunocompromised patients including those with HIV infection and malignancies and
- Disseminated varicella infection including pneumonia, encephalitis, severe hepatitis, or thrombocytopenia.

Intravenous acyclovir therapy is indicated for severe disease and for varicella in immunocompromised patients. Intravenous acyclovir (10 mg/kg or 1,500 mg/m² q 8 hours IV) initiated within 72 hours of development of initial symptoms decreases the progression of the disease in high risk patients. The treatment is continued for 7–10 days. The drug should be administered as an infusion and creatinine clearance should be monitored. Oral acyclovir (20 mg/kg/dose) given as 4 doses/day for 5 days should be used for the other indications mentioned above. Treatment should be initiated as early as possible, within 24 hours of rash and preferably not beyond 72 hours. The therapy is continued for 7–10 days or till no new lesion appears for 48 hours (**Table 1**).

Children with herpes-zoster generally have milder self-limited disease with minimal postherpetic neuralgia. Thus oral acyclovir may be reserved for use in healthy children who complain of severe pain or in immunocompromised children. The drug dosage and duration is the same as above.

Foscarnet (60–90 mg/kg/day) is the only available drug for acyclovir-resistant varicella. Experience with valacyclovir (prodrug of acyclovir) and famciclovir (prodrug of penciclovir) is limited in children.

Cloxacillin can be used to treat skin infections. More severe sepsis will require appropriate antibacterial chemotherapy which should be guided by swabbing of the affected lesions and by cultures of the blood and of any pus. Corticosteroids have no role in treatment of zoster.

Table 1 Acyclovir for treatment of varicella in immunocompetent children

Age group	Uncomplicated	Complicated*
Neonates	Intravenous acyclovir (10 mg/kg/dose), thrice a day. <i>Duration</i> : 14 days for skin/eye involvement, to 21 days for disseminated or CNS disease	
Infants (0–1 year)	Oral acyclovir (20 mg/kg/dose) given as four doses/day for 7–10 days	Intravenous acyclovir (10 mg/kg/dose or 1,500 mg/m ² q 8 hours IV) for 7–10 days
Children (1–13 years)	No antivirals	
Adolescents (> 13 years)	Oral acyclovir (20 mg/kg/dose) given as 4 doses/day for 7–10 days	

* Disseminated varicella infection including pneumonia, encephalitis, severe hepatitis, or thrombocytopenia.

PREVENTION

Active Immunization

Two doses of live virus vaccine (administered at 12–15 months, and 4–6 years) are recommended by the Indian Academy of Pediatrics to prevent varicella in healthy children. Protective efficacy of two-dose regimen is 98–100%. Varicella vaccine should not be given within 4 weeks of MMR vaccination; however, both can be given simultaneously.

Postexposure Prophylaxis

Varicella vaccine, if given within 3–5 days of exposure, can prevent or modify the disease in household contacts. Chemoprophylaxis with acyclovir is not an established mode of prevention.

Varicella zoster immunoglobulin (VZIG) 125 unit (U) is recommended for newborns whose mothers have varicella 5 days before to 2 days after delivery. Other susceptible high risk contacts (pregnant women, immunocompromised children, and those with malignancy or on steroids) should also be given VZIG (125 U for every 10 kg increment, to a maximum of 625 U).

HERPES ZOSTER

This condition represents reactivation of a latent VZV infection and occurs several years after primary infection with VZV and is less common in children. It is characterized by localized unilateral painful vesicular eruptions over 1–3 dermatomal segments (**Fig. 1**). The skin lesions are more pruritic and painful than varicella, though pain and severity is less in children as compared to adults. Some immunocompromised patients may experience protracted pain after healing of skin lesions (postherpetic neuralgia). They may have disseminated lesions mimicking varicella, pneumonia, hepatitis, or encephalitis. Severely affected HIV patients may develop a chronic relapsing cutaneous disease or central nervous system disease without rash. Around 4% patients may suffer a repeat episode of zoster. Subclinical zoster may also occur with dermatomal pain but no rash (*zoster sine herpette*).

PROGRESSIVE VARICELLA

Certain patients (immunocompromised patients, pregnant women or newborns) may experience a severe disease when fever and rash progression may continue for more than 2 weeks. Severe disease can be life-threatening, if associated

with disseminated intravascular coagulation or visceral organ dysfunction. Ominous signs include severe abdominal pain (involvement of mesenteric lymph nodes or liver) or appearance of hemorrhagic vesicles.

CONGENITAL VARICELLA

This is a constellation of defects which occur due to maternal VZV infection during first or second trimester, first described by LaForet and Lynch in 1947. There is a 2% risk to the baby for developing congenital varicella embryopathy following maternal infection in early gestation. Though most cases occur following maternal varicella, a small proportion is reported after maternal herpes-zoster infection. The hallmark of the disease is cicatricial scarring of the limbs—characterized by zigzag scarring of skin in dermatomal pattern with limb hypoplasia. The embryopathy is associated with (1) neurological features—cortical atrophy, microcephaly, seizures, mental retardation; (2) eye abnormalities—retinitis, microphthalmia, cataract; (3) digital defects, and (4) renal anomalies in few. The diagnosis is predominantly clinical and supported by historical clues. Viral DNA identification by PCR from tissue samples may be done; serology is not conclusive. There is no prophylactic role of varicella immunoglobulin or acyclovir administration to mother in antenatal period. Treatment of the newborn with acyclovir (after delivery) is not effective.

VARICELLA NEONATORUM

This condition results when a neonate born to mother with varicella infection acquires clinical varicella in the first few days after birth. If maternal rash develops more than 5 days before delivery, the virus may still be transmitted to the fetus, but clinical disease does not occur in the newborn due to simultaneous transfer of maternal VZV antibody (seen only after 30 weeks gestation). If the maternal rash appears less than 5 days before delivery or up to 2 days after delivery, there is 17–30% risk that the baby will receive a large inoculum without maternal antibody. Such babies are at a very high risk of disseminated disease with death (fatality rate can be as high as 30%, if not treated in time) from pneumonitis, and should be protected at birth by giving VZIG. In addition, all preterm less than 28 weeks with active maternal varicella during delivery should also receive VZIG. Neonatal varicella may still occur in 50% of these, despite VZIG administration; however, the disease is mild. If symptoms develop, the baby should receive acyclovir (10 mg/kg q 8 h) for 7–10 days. A neonate can also acquire varicella postnatally from the community and should also be treated with acyclovir. VZIG has no role once active infection has occurred.

BREAKTHROUGH VARICELLA

Varicella vaccine administered as a one-dose regimen to healthy children offers 85% protection (range 44–100%). Vaccinated children can thus suffer from varicella. Breakthrough varicella is defined as varicella occurring in a child who was vaccinated at least 42 days prior to eruption of the rash with one dose of varicella vaccine, and caused by wild type varicella virus. Rash occurring between 14 days and 42 days after vaccination can also be due to vaccine strains.

Breakthrough varicella is usually a mild disease (25% may still have florid rash). It is predominated by a maculopapular rash; vesicles are less frequent. Number of lesions is less than 50. These children are less likely to transmit the disease to others, i.e., the secondary attack rate of breakthrough varicella is lower than classical varicella. Recipients of two-dose varicella vaccine are less likely to have breakthrough varicella as compared to those having received one dose only.

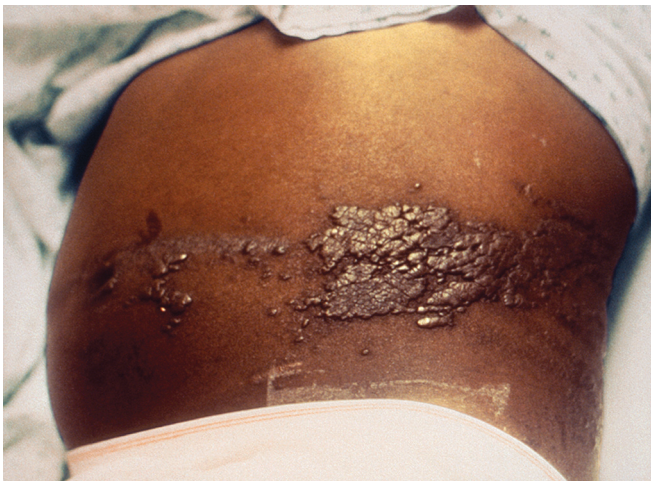


Figure 1 Herpes zoster

Source: Public Health Image Library (PHIL), CDC, USA.

IN A NUTSHELL

1. Chickenpox is caused by primary infection of VZV; reactivation, years later, results in zoster. Both varicella and zoster are highly contagious.
2. Man is the only reservoir. Natural infection provides lifelong immunity.
3. The typical varicella rash is pleomorphic, vesiculopustular and distributed in a centripetal pattern.
4. Period of infectivity ranges from 48 hours before the onset of rash till lesions have crusted (4–5 days).
5. Diagnosis is clinical; there is no role of laboratory investigations in routine diagnosis of chickenpox.
6. Disease is more severe in less than 1 year and more than 13 years age, and immunocompromised children.
7. Antiviral drugs are not routinely indicated for uncomplicated varicella in children 1–13 years age.
8. Acyclovir is used only in immunocompromised, neonates and complicated cases (meningoencephalitis, ataxia, ADEM, pneumonitis or other systemic complications).
9. Immunoprophylaxis with live attenuated vaccine is recommended for susceptible household contacts within 4 days of exposure. There is no role of chemoprophylaxis.
10. Neonates born to mothers, who develop varicella 5 days before or 2 days after delivery should receive 125 U of VZIG.

MORE ON THIS TOPIC

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Chapter 31.7

Parvovirus Infections

Jagdish Chandra, Anu Maheshwari

Human parvovirus B19 (B19) belongs to the *Erythrovirus* genus within the Parvoviridae family. This virus was first discovered in 1975 while routine screening of asymptomatic donors for hepatitis B virus. The clinical implications of this virus were noted in 1981. Sample 19 in panel B (hence the name parvovirus B19) was read as a false positive result on a counterimmunoelectrophoresis assay. B19 is the predominant parvovirus pathogen in humans. The B19 strain is the prototype strain for genotype 1. The other less common and more recently described erythroviruses infecting humans include genotype 2 (prototype strain, LaLi) and genotype 3 (prototype strain, V9). Genotypes 1 and 2 are typically found in western countries (e.g., USA and Europe), while genotype 3 is found primarily in sub-Saharan Africa and South America, but is spreading.

EPIDEMIOLOGY

Parvovirus B19 infection occurs worldwide. Cases may be sporadic or can occur in clustered outbreaks. Where reportable, communities have documented not only a seasonality to B19 infections, but also cycles of local epidemics with case numbers that can peak every 4–10 years. The percentage of people with measurable levels of B19-specific IgG increases with increasing age, with most individuals becoming infected during their school years. When considering women as a separate group, approximately 30–40% of pregnant women lack measurable IgG to B19 and are therefore presumed to be susceptible to B19 infection.

AGENT

Parvovirus B19 is a small (26 nm), nonenveloped, ssDNA (5.6-kb) virus. The only known host for B19 is humans. The virus replicates in erythroid progenitor cells (late erythroid cell precursors and burst-forming erythroid progenitors) of the bone marrow leading to inhibition of erythropoiesis, which can result in anemia. The observed tropism of parvovirus is most likely due to the distribution of its cellular receptor, P blood group antigen. It is a globoside, which is found in high concentrations on red blood cells and their precursors. Rare individuals who lack P antigen are resistant to infection with parvovirus.

TRANSMISSION

Infected patients are most contagious during the phase of active viral replication and viral shedding, which occurs approximately 5–10 days after the exposure. During this phase, patients can be asymptomatic or present with nonspecific flu-like illness. It is not until the second phase of parvovirus infection that a person can present with specific symptoms or signs (e.g., arthralgia, arthritis, and/or an exanthem) specific to B19 infection. This is also the phase in which B19-specific antibody production and B19 antigen-antibody immune complex formation occurs. Individuals are no longer infectious when exhibiting these clinical characteristics. Patients having weakened immune systems may be contagious for a longer amount of time. There are three documented modes of transmitting B19:

1. *Respiratory transmission* is the most common way an individual acquires this virus. It is transmitted through close person-to-person contact, fomites, and respiratory secretions and/or saliva. Young children are the main source of respiratory acquired B19. This scenario places pregnant women with young children at home at high risk of becoming infected.

2. *Vertical transmission* can occur if a susceptible woman becomes infected during her pregnancy. The risk of a poor outcome for the fetus is greatest when the congenital infection occurs within the first 20 weeks of gestation.
3. *Transmission* can occur from transfusion of blood or blood products containing B19 (transfusion transmitted). Individuals requiring regular infusions of blood product(s) that are made from large plasma pools (albumin, IVIG) are at greatest risk for acquiring the virus compared to those individuals receiving single units.

PATHOGENESIS

Viremia occurs 7–10 days after exposure to the source and usually lasts approximately 5 days. The virus titer peaks in the first few days of infection and can reach or exceed 10^{12} particles per mL of blood. Parvovirus B19-specific IgM antibodies are detected as early as day 10–12 of illness and can persist for up to 5 months. Specific IgG antibodies are detectable about 15 days postinfection and persist long-term. The close timing that exists between developing B19-specific IgM and IgG antibodies means that it is rare to find an IgM-positive serum sample that is not also IgG-positive. Antibodies to VP1 are required for an effective immune response. The humoral antibody response is the major pathway that is responsible for virus clearance and subsequent protection from disease.

Parvovirus B19 infection also elicits an inflammatory cell-mediated immune response, including the production of tumor necrosis factor (TNF)-alpha, interferon (IFN)-gamma, interleukin (IL)-2 and/or IL-6. A striking CD8 T cell response was maintained and eventually increased over several months after the resolution of illness. The importance of cellular immunity is also suggested by clinical reports of remission of parvovirus induced anemia after initiation of highly active antiretroviral therapy in advanced AIDS patients.

CLINICAL FEATURES

The clinical presentations associated with B19 infection vary greatly, ranging from benign to life threatening (**Table 1**). The clinical presentation is influenced by the infected individual's age and hematologic and immunologic status. There are five well-established syndromes associated with B19 infection: (1) Fifth disease; (2) Arthropathy; (3) Nonimmune hydrops fetalis, intrauterine fetal death, or miscarriage; (4) Transient aplastic crisis in those with chronic hemolytic disorders; and (5) Chronic pure red blood cell aplasia (B19PRCA) in immunocompromised individuals. A wide range of other syndromes have been reported to be associated with B19 infections, but a causal role for the virus has yet to be conclusively established (**Table 2**).

Erythema Infectiosum

Erythema Infectiosum (EI) often occurs in outbreaks among school-aged children, although it can occur in adults as well. EI is also referred to as *fifth disease* since it represents one of six common childhood exanthems, each named in order of the dates they were first described. The illness begins with nonspecific prodromal symptoms, such as fever, coryza, headache, nausea, and diarrhea. These constitutional symptoms coincide with onset of viremia. Two to five days later, the classic erythematous malar rash appears (the so-called slapped cheek rash) with relative circumoral pallor. This facial rash (**Fig. 1**) is often followed by a reticulated or lacelike rash on the trunk and extremities (**Fig. 2**). The estimated incubation period from exposure to the onset of rash has usually been between 1 and 2 weeks but can be as long as 3 weeks. By the time the rash develops, viremia has resolved and the child usually feels well. The rash is thought to be immunologically mediated. A typical feature of EI is recrudescence of rash after a variety of nonspecific stimuli,

Table 1 Symptoms and signs of parvovirus B19 infection in children

Symptoms or sign	Frequency (%)
Fever	14–53
Headache	12–53
Sore throat	12–60
Pruritus	0–>50
Cough	5–40
Diarrhea	0–40
Nausea/vomiting	0–33
Coryza/conjunctivitis	4–27
Arthritis/arthritis	0–9

Table 2 Conditions associated with parvovirus infection

Cardiovascular
• Acute heart failure
• Myocarditis
• Pericarditis
• Pericardial effusion
Cutaneous
• Gianotti-Crosti syndrome
• Papular-purpuric gloves and socks syndrome
• Vascular purpura
• Erythema nodosum
• Erythema multiforme
• Livedo reticularis
Hematological
• Aplastic anemia
• Autoimmune hemolytic anemia
• Chronic neutropenia
• Thrombocytopenic purpura
• Transient erythroblastopenia of childhood
Neurological
• Brachial plexus abnormalities
• Meningitis/encephalopathy
• Seizures
• Sensorineural abnormalities
Rheumatological
• Vasculitis
• Juvenile idiopathic arthritis
• Systemic lupus erythematosus
• Rheumatoid arthritis
Renal
• Proliferative glomerulonephritis
• Collapsing nephropathy
• Post-transplant anemia, pancytopenia
• Nephrotic syndrome in sickle cell disease

such as change in temperature, exposure to sunlight, exercise, or emotional stress.

B19 infection has also been associated with other types of rashes including morbilliform, confluent, and vesicular rashes. In the Gianotti-Crosti syndrome, a papulovesicular acrodermatitis may be accompanied by severe pruritus. Parvovirus B19 DNA was also identified by polymerase chain reaction in a cutaneous biopsy specimen of a patient with papular-purpuric *gloves and socks* syndrome, an illness characterized by pruritic painful acral erythema associated with fever and mucosal lesions. Although proposed as an etiologic agent, parvovirus was not linked to Henoch-Schönlein purpura in children in one case control study.

The pathogenesis of the rash associated with B19 infection is not clear. However, since it usually coincides with measurable



Figure 1 Left side of this boy's face displaying slapped cheek appearance rash of erythema infectiosum, or *Fifth disease*
Source: Public Health Image Library (PHIL), CDC, USA.



Figure 2 Hands of a school boy showing skin lesions of erythema infectiosum, or *Fifth disease*
Source: Public Health Image Library (PHIL), CDC, USA.

serum antibody production, it is presumed to be at least partially immune mediated. The role of serum antibodies in rash development is also suggested by the appearance of rash after IVIG administration to immunodeficient patients with chronic infection. Immune complexes have been detected during acute infection and are proposed to participate in the pathogenesis of the disease. B19 DNA and antigen have been detected in a skin biopsy specimen from a patient with EI, suggesting that direct infection of epidermal cells may also contribute to rash development. Approximately 75% of patients will develop a rash, although less than 20% will have the appearance of the typical malar (*slapped cheeks*) rash seen in EI.

Arthritis

Parvovirus B19 infection can present as an acute arthritis and may be mistaken for acute rheumatoid arthritis in the absence of rash. Arthralgia and/or arthritis are more common in adult females compared to adult males or children. Joint symptoms are usually symmetric and most frequently involve the small joints of the hands, wrists, knees, and feet. Joint symptoms usually resolve in three weeks, although a minority of patients may develop persistent

or recurring arthropathy. The arthritis associated with acute B19 infection does not cause joint destruction.

Hematologic Manifestations

Parvovirus B19 infection can lead to transient aplastic crisis and chronic anemia, depending on the host.

Transient Aplastic Crisis

Individuals with hematologic abnormalities, including increased RBC destruction (e.g., sickle cell disease, hereditary spherocytosis) or decreased RBC production (e.g., iron deficiency anemia) are at increased risk of developing transient aplastic crisis (TAC) secondary to parvovirus infection. Genotype 3 erythroviruses have also been associated with TAC. Patients with TAC usually present with pallor, weakness and lethargy secondary to severe anemia. Infection can rarely be fatal due to congestive heart failure, cerebrovascular accidents, and acute splenic sequestration. These patients usually do not have the characteristic rash. However, they often have an undetectable peripheral reticulocyte count and a drop in hemoglobin concentration of more than 30% secondary to complete arrest of erythropoiesis.

Chronic Anemia in Immunocompromised Hosts

Immunosuppressed patients are at risk of developing acute or chronic anemia following B19 infection due to lack of protective antibodies. Life-threatening anemia can develop due to the inability to mount an immune response to clear viremia. Chronic infection leads to chronic hypoplasia or aplasia of the erythroid series in the bone marrow, resulting in giant pronormoblasts and a reticulocytopenic anemia. Infection is usually not accompanied by rash or arthropathy, which may be due to the inadequate immune response in this patient population. Chronic infection and anemia have been described in leukemia, HIV, congenital immunodeficiency and recipients of organ transplants. Immunosuppressed patients respond well to intravenous immune globulin (IVIG); however, some patients require recurrent treatment for relapses. Resolution of parvovirus-induced anemia in HIV-infected patients after the initiation of highly active antiretroviral therapy has also been reported.

Parvovirus in Malaria-Endemic Areas

Severe anemia is a major cause of death among young children in developing countries and may be due to a variety of causes, including malaria, iron deficiency, and hookworm infections. Acute B19 infection is associated with an increase in the risk of severe anemia comparable to that associated with *Plasmodium falciparum*. The pathogenesis of anemia is due to direct destruction of erythrocyte progenitor cells, which dramatically reduces red cell production. During an acute infection, this results in a significant drop in hemoglobin. In healthy individuals, RBC production returns in 10–14 days with little anemia. However, in individuals with an increased RBC turnover, even a limited cessation of RBC production can lead to a clinically significant drop in hemoglobin and TAC. In patients unable to control B19 infection because of immunosuppression or immunodeficiency, lysis of RBC precursors leads to prolonged cessation of RBC production and the development of a severe, chronic pure red cell aplasia and anemia.

Nonimmune Hydrops Fetalis and Intrauterine Fetal Death

B19 infection during pregnancy can result in fetal complications including miscarriage, intrauterine fetal death and/or nonimmune hydrops fetalis. The fetus is especially susceptible to the effects of B19-induced anemia due to its shortened RBC half-life and the expanding RBC volume. The relatively immature fetal immune system is also less able to effectively control virus infection. The

ensuing fetal hydrops appears to result from the onset of severe anemia, which in turn causes high output heart failure. Fetal B19 infection can also present with thrombocytopenia.

Myocarditis

Parvovirus B19 infection has been associated with myocarditis, dilated cardiomyopathy, and isolated left ventricular diastolic dysfunction. Fatal myocarditis secondary to parvovirus B19 infection has also been described in a liver transplant recipient.

Renal Disorders

The possibility of a link between B19 infection and glomerular disease has been suggested from numerous case reports that describe onset of nephritis or nephrotic syndrome after onset of parvovirus infection. Several case reports have linked acute B19 infection to nephrotic syndrome in patients with sickle cell disease. Thrombotic microangiopathy, hemolytic uremic syndrome, and renal involvement in association with systemic vasculitides such as Henoch Schönlein purpura, polyarteritis nodosa and Wegener granulomatosis have also been associated with B19 infection. Case reports implicate parvovirus in the pathogenesis of proliferative glomerulonephritis and collapsing glomerulopathy, but a causal relationship has not been established. A proposed role for B19 infection is based on the temporal association of renal findings with viral infection, positive serology, and identification of the viral genome in the glomerulus. Patients who require dialysis may have increased susceptibility to acute and chronic anemia after parvoviral infection. Factors that predispose this population to complications of B19 infection include impaired immune response, deficient erythropoietin production, and possibly decreased erythrocyte survival. Chronic anemia and pure red blood cell aplasia are the most common complications of parvovirus infection in the postrenal transplant cases.

Other Disease Associations

B19 has been reported in association with a wide range of diseases, including arthritis, vasculitis, myocarditis, nephritis, lymphadenitis, idiopathic thrombocytopenic purpura, meningitis and encephalitis, hemophagocytic syndrome, and fulminant liver disease as well as many other conditions. Parvovirus B19 is also a recognized cause of isolated angioedema in neonates.

APPROACH TO DIAGNOSIS

The B19 immune status varies with acute infection, previous infection, and reactivation of infection.

Acute Infection

The choice of diagnostic testing for acute B19 infection will depend on the patient's immune status. In immunocompetent individuals, the preferred method is serologic testing to detect circulating B19-specific IgM and IgG antibodies. However, in the immunosuppressed patient, or for congenital infections, nucleic acid amplification testing (NAAT) is recommended. Detectable levels of B19-specific IgM can be found within 7–10 days of virus exposure and remain measurable for several months before diminishing. In some patients, B19-specific IgM antibodies can persist for six months or more. Therefore, the presence of these antibodies, especially at low titers, is suggestive but not conclusive proof of recent infection.

Acute infection can also be diagnosed by demonstrating a fourfold or greater rise in serum B19-specific IgG antibody titers. However, since this procedure requires two separate time points for sample collection, it is considered impractical in most clinical situations. Today, most serology testing will include concurrent analyses for both B19-specific IgM and IgG antibodies from a single blood sample. At present, NAAT is considered the most sensitive approach for direct detection of virus within a specimen,

and is the test of choice for diagnosing acute infection in the immunocompromised patients, including the fetus and neonate.

Previous Infection

Previous infection is best confirmed by serologic testing that detects B19-specific IgG antibodies. Documenting previous infection, which infers immunity, is a common practice in obstetrics when the physician is concerned about the immune status of a pregnant woman who has a history of exposure to an individual infected with B19, especially if the contact is her own school-aged or younger children.

Reactivation of Infection

Reactivation of persistent infection can occur in immunocompetent and, more often, immunocompromised individuals. These infections are confirmed by demonstrating the presence of the virus for a prolonged period. This is most often accomplished by NAAT to detect B19 DNA within a specimen. Individuals with persistent infection may also have measurable levels of B19-specific IgM antibodies over time if they are healthy enough to produce immunoglobulin. Unlike NAAT, serology testing does not appear to differentiate between the genotypes, as the level of divergence among the strains at the amino acid level is significantly less than that seen at the nucleotide level. Appropriate clinical specimens for NAAT analysis include serum, plasma, bone marrow, amniotic fluid, and placental and fetal tissues. As with any diagnostic test, NAAT can produce false positive and/or false negative results.

Antigen Detection

Immunohistochemical (IHC) techniques can be used to detect B19 antigens in a variety of tissues, especially fetal and placental tissues.

Virus Isolation

Freshly harvested bone marrow or fetal cord blood, or several continuous cell lines can support low level B19 replication in vitro. However, these in vitro systems have not been used for clinical applications.

MANAGEMENT (TABLE 3)

Treatment of Acute Infection

Treatment of symptomatic B19 infection varies with the clinical manifestation. Erythema infectiosum (*fifth disease*) is a self-limited, mild illness most often occurring in children. There is no specific therapy and usually no indication for symptomatic treatment. In some patients, symptomatic therapy for arthralgia, arthritis, or pruritus may be indicated. Nonsteroidal anti-inflammatory drugs can provide symptomatic relief. There is limited data to support the use of IVIG treatment for B19-associated arthropathy. The anemia in TAC is often severe enough (hemoglobin levels below 6 g/dL with few or no reticulocytes) to require transfusion until the patient's immune response eliminates the infection and red cell production returns. The usual course of parvovirus associated anemia is spontaneous resolution within a few days to weeks.

Treatment of Chronic Infection with Anemia

Most patients with chronic B19 infection and anemia have received immunosuppressive therapy for cancer, leukemia, or tissue transplantation, have a congenital immunodeficiency or have HIV-associated immunodeficiency. Most of these reports have occurred prior to the availability of potent antiretroviral therapy (ART). Even in the absence of immunodeficiency pure red cell aplasia has been described. The anemia usually responds to IVIG treatment with a reticulocytosis within one week, and the chronic viremia was cured after periodic IVIG infusions over four months. In such cases it may be warranted to look for in vitro abnormalities in T- and B-cell function.

Table 3 Treatment options for symptomatic parvovirus B19 infection

Manifestation	Treatment options
Erythema infectiosum	None or symptomatic
Arthritis or arthralgia	NSAIDs
Transient aplastic crisis	Transfusion and oxygen if needed
Fetal hydrops	Intrauterine blood transfusion (?)
Chronic infection with anemia	IVIG and transfusions
Chronic infection without anemia	IVIG (?)

Abbreviation: IVIG, intravenous immunoglobulin.

Patients have been treated with several different IVIG regimens, such as 400 mg/kg of commercial IVIG for 5 or 10 days or 1000 mg/kg for 3 days, both with good results. Relapses in these patients have been successfully treated with maintenance IVIG at doses of 0.4 g/kg/day every four weeks.

Treating Chronic Infection without Anemia

Chronic B19 infection has been demonstrated in patients without anemia or underlying immunodeficiency. It is not clear if IVIG treatment is helpful in this setting.

PREVENTION

The best measures currently available to prevent B19 infection are those designed to interrupt transmission by good infection control practices. A recombinant human parvovirus B19 vaccine, composed of the VP1 and VP2 capsid proteins was evaluated in a randomized, double-blind, phase 1 trial. In 2007, a phase I/II trial was undertaken to assess the safety and immunogenicity of a recombinant B19-parvovirus vaccine. However, this study has been suspended due to vaccine-associated adverse events.

IN A NUTSHELL

1. Parvovirus B19 replicates in erythroid progenitor cells of the bone marrow and blood leading to inhibition of erythropoiesis.
2. Viremia occurs one week after exposure and usually lasts approximately 5 days, with virus titers peaking on the first few days of infection. Development of a robust antibody response corresponds to viral clearance and subsequent protection from disease.
3. There are five well-established syndromes associated with B19 infection: (1) Fifth disease (erythema infectiosum), (2) Arthropathy; (3) Nonimmune hydrops fetalis, intrauterine fetal death, or miscarriage; (4) Transient aplastic crisis in those with chronic hemolytic disorders; and (5) Chronic pure red blood cell aplasia (B19-PRCA) in immunocompromised individuals.
4. In children, EI begins with nonspecific prodromal symptoms, followed by a classic erythematous malar rash and lacy appearance on the extremities.
5. B19 infection during pregnancy can result in fetal complications including miscarriage, intrauterine fetal death and/or nonimmune hydrops fetalis.
6. There is no specific antiviral drug currently available for treating patients infected with B19. Likewise, no vaccine exists for preventing the infection.
7. In most instances, treatment is directed toward symptoms but in some instances antiviral treatment with IVIG is indicated. Until a vaccine is developed and becomes available, good hygienic practices should be the focus of prevention strategies.

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Chapter 31.8

Roseola Infections

Swati Singhal

Human herpes virus 6 (HHV 6) and Human herpes virus 7 (HHV 7) are human pathogens of emerging clinical significance. HHV 6 was first isolated from patients with lymphoproliferative disorders in 1986. It was established to be a causative agent of roseola infections in 1988. HHV 7 is known since 1990 and bears many similarities with HHV 6. It is postulated that most clinical infections by HHV 6 are caused by the HHV 6 B variant. Roseola infantum, also known as *exanthem subitum*, refers to the prototype exanthematous illness caused by HHV 6. HHV 6 infections are ubiquitous in children less than 2 years of age.

EPIDEMIOLOGY

Infections by HHV 6 are known to occur across all geographical regions with no seasonal variations and no known outbreaks. For reasons that are not yet clear, it is reported more frequently from Japan. There is no local Indian data available but it is felt to be a common childhood exanthematous illness. Neonates and infants younger than 6 months have transplacentally acquired antibodies and are immune to infection. Subsequently, passive immunity starts to fade and the child gets prone to develop infection. The most common age group to get affected is from 6 months to 15 months of age. The immunity after primary infection is usually lifelong. Immunological studies indicate that almost 90% adults are seropositive for infection. It is possible for infection to get reactivated in immunocompromised states.

ETIOLOGY

Not all HHV 6 infections are roseola and not all roseola infections are caused by HHV 6. Roseola infections are commonly caused by HHV 6 and less commonly by HHV 7. A minority of roseola infections are caused by Echovirus 16. It is noteworthy that roseola is the most prototypical but not the most common clinical manifestation of HHV 6. The most common manifestation of HHV 6 in immunocompetent infants is a nonspecific febrile illness.

PATHOGENESIS

HHV 6 is distinguished into two forms as HHV 6 A and HHV 6 B based on distinct genetic, immunological and biological features. HHV 6 B variant accounts for the majority of clinical disease conditions. The exact role of HHV 6 A in disease states is unclear but it is postulated that it might cause severe illness in immunocompromised individuals. HHV 7 is closely linked to HHV 6 B and its pathogenetic mechanism is very similar to HHV 6 B. The exact mode of transmission for these viruses is unclear. It is postulated that they are shed in the saliva of healthy adults. The infection is possibly acquired through oral/nasal or conjunctival mucosa. The virus eventually establishes itself mainly in circulating CD4 T lymphocytes, but also in macrophages, dendritic cells, fibroblast, epithelial cells and bone marrow progenitors. It has been demonstrated that congenital transmission of HHV 6 takes place in approximately 1% of newborns, but the clinical significance of this is yet to be established. The exact mechanisms of the characteristic rash of roseola infantum are not known.

CLINICAL FEATURES

Infections in Immunocompetent Individuals

This group accounts for the vast majority of children affected with HHV 6 and HHV 7. The infection can be described in two stages. The *prodromal stage* consists of nonspecific and variable presence of malaise and other viral prodromes like rhinorrhea and pharyngeal injection. This is followed by the *febrile stage* which typically consists of high grade fever, but the child is otherwise well. There could be mild edema of eyelids and posterior cervical lymphadenopathy. Infants in Asian countries might develop ulcers at the uvulopalatal junction, known as Nagayama spots. Up to 5–10% children might experience febrile seizures in this stage. The fever usually lasts for 2–3 days and often ceases abruptly (crisis), sometimes to subnormal levels. Occasionally, the fever might take time to subside (lysis). In most cases, the disease process is limited to this stage. There are usually no further complications and the episode might be clinically diagnosed as a nonspecific febrile illness. *In 30% children, the febrile phase is followed by the onset of a sudden rash.* The rash is a discrete maculopapular rash, starting from the trunk and spreading to rest of the body. The rash is nonitchy and there are typically none to minimal systemic features. The rash subsides in another 2–4 days' time. It is this clinical presentation of a febrile stage followed by a characteristic rash which is known as Roseola Infantum or Exanthem Subitum (*Subitum* refers to *rapid* in Latin language).

In a large prospective study involving emergency hospital visits for febrile children less than 3 years of age, primary HHV 6 infection accounted for 10% of overall cases and 21% cases in the age group of 6–12 months. Thirteen percent of these children had febrile seizures and these accounted for 33% of all children with febrile seizures less than 2 years of age. *Febrile seizures are the most common central nervous system manifestation of primary HHV 6 infection.* The exact mechanism of this is not known but could be a result of direct invasion by the virus. Rarely, the manifestations could be more severe and result in bulging fontanel, meningoencephalitis or encephalopathy.

Usually, the illness runs a benign course, but there have been occasional case reports of infants developing thrombocytopenia, granulocytopenia, fulminant hepatitis and disseminated infection. Primary infection after the age of 2 years is rare. It most commonly presents as infectious mononucleosis like illness or an undifferentiated febrile illness. HHV 6 B has been implicated in the pathogenesis of many other medical disorders like multiple sclerosis, chronic fatigue syndrome, Hodgkin and non-Hodgkin lymphomas, leukemia and myocardial dysfunction, but the exact causative role is yet to be established. It is also postulated that HHV 6 infection might be contributing to the development of severe drug hypersensitivity syndrome. The direct consequences of HHV 6 A infection are not known.

The illness caused by HHV 7 is clinically indistinguishable from HHV 6 illness. Epidemiologically, HHV 7 might affect slightly older children (median age 22 months with HHV 7 and 9 months with HHV 6) and the duration of fever might be shorter with slightly lower mean temperatures.

Infections in Immunocompromised Individuals

Since HHV 6 and HHV 7 establish latent infection in leukocytes, they play important role in disease causation in immunocompromised hosts. There has been extensive evidence to suggest that HHV 6 infections can lead to serious disease in children with HIV, organ transplant and stem cell transplant recipients. The illness could range from an undifferentiated febrile illness to more serious and localized infections like encephalitis, bone marrow suppression and interstitial pneumonitis. Fatalities have been reported due to these

complications. The disease process in such patients most likely represents reactivation of a previously acquired infection. Most infections are caused by HHV 6 B, but recent case reports suggest that HHV 6 A might also cause giant cell hepatitis and fatal disease. HHV 6 and HHV 7 have been shown to have immunomodulatory properties and might have an indirect effect on viral infections (especially CMV), fungal infections and allograft rejection.

DIAGNOSIS

It is vital to establish the *sequence of symptoms* when evaluating a child with a febrile exanthematous illness. *The distinct history of 3 days of sustained fever in a child 6–15 months age, followed by appearance of a maculopapular eruption after subsidence of fever, is very characteristic of roseola infections.* If the infant is seen during the febrile stage of the illness, it might be difficult to distinguish it from other viral and bacterial illnesses. One noteworthy feature is the nontoxic appearance of the infant, despite the high grade fever. The occurrence of a seizure at this stage might mimic meningoencephalitic illness and might warrant close supervision and appropriate management. This might include admitting the child and further investigations.

If the infant is seen during the exanthematous stage, the presence/absence of other systemic features is crucial. The absence of fever at this stage is likely to be a result of HSV 6/HSV 7 infection. In infants who receive antibiotic treatment during the high grade febrile phase of illness, and subsequently develop a rash, it might be difficult to ascertain if the rash is due to roseola or due to drug eruption. Drug rashes are usually morbilliform and pruritic and resolve well after discontinuing the antibiotic. However, if the infant is still febrile when the rash is present, and has associated features, it is unlikely to be due to roseola. In the Indian context, it is crucial to be able to distinguish more serious illnesses like measles and rubella. Measles is characterized by the appearance of the rash at the *height of the febrile phase and the presence of associated features* like conjunctivitis, cough and rhinorrhea in a *sick looking child*. Another viral illness that needs to be differentiated is rubella. Rubella is characterized by *low grade fever* and the presence of *distinct prodromal features*. The rash in rubella also tends to be more extensive and confluent than that of roseola. In most cases, *a sound clinical judgment based on history and a thorough clinical examination is all that is required to establish the diagnosis of roseola infections.* The diagnosis can be confirmed by serodiagnosis and isolation of the virus by viral culture, antigen assays, and polymerase chain reaction (PCR). Seroconversion is often used to establish the diagnosis in primary infections. Other investigations are difficult and hence might be difficult to carry out in a resource constrained setting.

Blood investigations might reveal leukopenia and relative lymphocytosis, which might help differentiate from other serious bacterial illnesses. The cerebrospinal fluid (CSF) analysis in infants presenting with febrile seizure is usually normal. In the event of encephalitis or meningoencephalitis, the CSF might show mild pleocytosis and slightly high protein levels.

MANAGEMENT

The generally benign and self limiting nature of HHV 6 and HHV 7 infections in immunocompetent infants implies that supportive treatment is all that is required with no role of routine antiviral therapy. Fever can be managed by tepid water dressings and antipyretics. The infant might need supplemental feeds to prevent dehydration. Reassurance to caregivers is of utmost importance. They should be informed regarding the disease process and no necessity for antibiotics or antiviral drugs. Also,

they need to be updated that most of the older children and adults are immune to infection. A follow-up visit should be arranged within the next 48 hours to ensure due recovery of the infant.

The treating physician needs to be aware of the risk of serious disease in immunocompromised children. No standard antiviral treatment regimens are available, but most studies report using ganciclovir, foscarnet and cidofovir (either alone or in combination) for treatment of severe complications in this susceptible group. However, there is no role of routine chemoprophylaxis to prevent HHV related disease.

PROGNOSIS

Most infants do extremely well after recovering from the febrile and/or the rash phase. There are no long-term sequelae in immunocompetent children. Immunocompromised children might have severe and occasional fatal disease outcomes.

PREVENTION

Currently, there are no guidelines so as to prevent HHV 6 and HHV 7 transmission as HHV 6 infection is considered to be ubiquitous in children less than 2 years of age. There is no role of prophylaxis even in high risk patients.

IN A NUTSHELL

1. HHV 6 and HHV 7 usually cause benign viral illness.
2. It usually affects children less than 2 years of age and has a distinct pattern of high grade fever followed by rash on resolution of the fever.
3. It is important to be able to clinically distinguish it from other serious viral and bacterial illnesses.
4. Treatment is mainly supportive in immunocompetent individuals.
5. The treating physician needs to be aware of disease complications in high risk groups.

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Chapter 31.9

Viral Hepatitis

Amit Goel, Chhavi Nanda

Hepatitis means inflammation of the liver irrespective of its cause, severity or duration. It is often associated with yellow discoloration of eyes and urine and elevated serum levels of liver enzymes, i.e., alanine aminotransferase (ALT) and aspartate aminotransferase (AST), though a subset can be asymptomatic. The most common cause is infection with one of the hepatotropic viruses; other causes are nonhepatotropic viruses (cytomegalovirus, herpes-simplex, varicella-zoster, dengue virus), bacterial agent (*Salmonella typhi*), parasites (*Plasmodium* species), drugs (antitubercular, anti-epileptic, halothane), ischemia (ischemic hepatitis), autoimmune conditions (autoimmune hepatitis), etc. The five known hepatotropic viruses [called hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus (HDV), and hepatitis E virus (HEV), respectively] affect primarily the liver, and thus present mainly with liver disease; the term *viral hepatitis* is usually reserved for infection with these viruses.

The infection and liver injury can be either short lasted (*acute*) or prolonged (chronic, empirically defined as > 6 months). HAV and HEV cause only acute viral hepatitis (AVH). In contrast, infection with HBV, HCV or HDV may lead to chronic or persistent infection, resulting in chronic viral hepatitis.

EPIDEMIOLOGY

Viral hepatitis occurs in all parts of the world, though its burden is higher in resource-poor countries in Asia and Africa, primarily because of high population density, poor water quality and sanitation, financial constraints, and lack of education and awareness. In India, HAV and HEV infection are very common. Nearly 1–3% of Indian population has chronic HBV infection and nearly 0.5–1.5% has chronic HCV infection. About 10–20% of chronic HBV infected individuals carries simultaneous HDV infection. In India, jaundice accounts for 1.5–2.2% of all hospitalizations.

ETIOLOGY

Hepatotropic viruses A to E differ markedly in their structure, epidemiology, host predilection, routes of transmission, incubation period, clinical presentations, natural history, diagnosis, and preventive and treatment options (**Table 1**).

Hepatitis A virus accounts for over 60% of cases with acute viral hepatitis or acute liver failure in Indian children. Over 90% of children have evidence of HAV infection by adolescence. Majority of HAV-infected children below 2 years are asymptomatic whereas children above 5 years are symptomatic. It is noteworthy that HAV related AVH in adults is more severe and carries rather higher risk for acute liver failure (ALF).

Hepatitis B virus causes acute as well as chronic infection and is the most common hepatotropic viral cause for liver cirrhosis and hepatocellular carcinoma in Asia, including India. Following HAV, HBV is the second most common hepatotropic virus causing AVH in children in India.

Table 1 Salient features of various hepatotropic viruses and associated disease

Feature	Virus				
	HAV	HBV	HCV	HDV	HEV
Virus size (nanometer)	28	42	50	35–37	32–34
Nucleic acid	RNA	DNA	RNA	RNA	RNA
Disease frequency in children and epidemiology	Most common cause of AVH in childhood	Second most common cause of AVH in childhood	Uncommon	Uncommon in India	Infrequently cause for AVH in children
Usual routes of transmission	Fecal-oral	Parenteral, mother-to-infant, sexual	Parenteral, mother-to-infant, sexual	Parenteral, sexual	Fecal-oral
Incubation period (d)	14–28	45–180 (usually 60–90)	15–150	30–180	15–60
Clinical syndromes	Acute viral hepatitis Acute liver failure (infrequent)	Acute viral hepatitis Chronic hepatitis Acute liver failure (infrequent)	Chronic hepatitis (very uncommon in children) Acute viral hepatitis (extremely infrequent)	HBV-HDV co-infection HDV super-infection in persons with chronic HBV infection	Acute viral hepatitis Acute liver failure (infrequent) Chronic hepatitis (very rare; not reported from India)
Chronicity and complications	No	Yes; may lead to cirrhosis and liver cancer	Yes; may lead to cirrhosis and liver cancer	Yes, with chronic HBV infection	Rare, in transplant recipients and immunosuppressed persons
Diagnostic test(s)	IgM anti-HAV Antibody	HBsAg (acute/chronic) IgM anti-HBc antibody (acute infection)	Anti-HCV and HCV RNA	IgM anti-HDV antibody, HDV RNA	IgM anti-HEV antibody
Treatment	None	Oral nucleoside analogs, or interferons	Combination of pegylated interferon and ribavirin; newer directly-acting anti-viral agents	Pegylated interferon	None for acute hepatitis Ribavirin for chronic infection
Vaccine	Yes	Yes	None	Yes (HBV vaccine)	Developed; not yet commercially available in most of the world

Abbreviations: HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus; HEV, hepatitis E virus; RNA, ribonucleic acid; DNA, deoxyribonucleic acid; AVH, acute viral hepatitis.

Hepatitis C virus related AVH is extremely rare. HDV infection can occur only in the presence of HBV infection, either simultaneously with acquisition of HBV (HBV-HDV coinfection) or as a piggy-back infection in persons with pre-existing chronic HBV hepatitis (HDV superinfection).

Hepatitis E virus is uncommon in children but is the most common cause of AVH and ALF in adults in India. Acute hepatitis E is uncommon in children particularly before adolescent age. This is possibly because HEV infection in children is most often asymptomatic.

PATHOGENESIS

Hepatitis A virus and HEV enter the body by oral route through fecal contamination of food and water, multiply in hepatocytes, followed by excretion in stool for a variable period of time. Person to person transmission is common with HAV but not with HEV. They have no cytopathic effect on hepatocyte, i.e., they do not destroy infected hepatocyte. Hepatocyte damage is the result of bystander injury during the natural immunity attempting to clear virus. Infiltrating lymphocyte in an attempt to clear virus from body, kills infected hepatocyte which result in various clinical and biochemical manifestations of liver injury such as serum transaminase elevation, jaundice, coagulopathy, liver failure, etc. Acute hepatitis is characterized by widespread hepatocyte necrosis followed by regeneration without leaving any stigma of previous disease.

Hepatitis B virus, takes advantage of being a DNA virus, enters into hepatocyte nucleus and integrates with host DNA thus forming covalently closed circular DNA (cccDNA), which remains inside the body for rest of the host's life. This causes chronic HBV infection.

About 70% of HCV infection leads to chronic infection. Several mechanisms are proposed which helps HCV to deceive the natural immunity and establish chronic infection in majority. Few of those mechanisms include high degree of genetic variability thus forming HCV quasi-species, mutations leading to altered innate immune cell functions, genetic susceptibility to HCV infection, impaired adaptive immune response, impaired antigen presenting cell function and failure to generate HCV specific T-cells.

On histopathology, chronic viral hepatitis, irrespective of viral cause, is characterized by infiltration with inflammatory cells (predominantly lymphocytes), ongoing necro-inflammation, variable amount of liver fibrosis and development of regenerating nodules, which together lead to progression to cirrhosis.

CLINICAL FEATURES

Hepatotropic virus infection may take three possible courses which, in order of frequency, are AVH, chronic viral hepatitis, and ALF. Acute viral hepatitis is a syndrome common to infection with all hepatotropic viruses. It typically runs a tri-phasic course: prodromal, icteric, and convalescent phases. All the patients may not evolve into icteric phase. Different phases are discussed here briefly, and more details are included in **Table 2**.

Prodromal phase Anorexia is the hallmark of prodromal phase, particularly in children. This phase lasts for a few days, but may occasionally extend to 3 weeks. Serum alanine aminotransferase/aspartate aminotransferase (ALT/AST) levels are the maximum at this phase. However, the degree of ALT/AST elevation has no relation with disease severity or outcome. Occasional child may worsen to ALF. Every hepatitic prodrome is not necessarily followed by icteric phase, particularly with HAV infection.

Icteric phase It follows viral prodrome and is heralded by yellow discoloration of eyes and urine. Onset of jaundice is often associated with improvement of the prodromal symptoms and appetite. The jaundice lasts for a variable period of a few weeks.

Convalescent phase Most of the children with AVH achieve complete clinical and biochemical recovery during this phase. This is the rule with HAV and HEV infection.

A minority of children with HBV infection and a majority of those with HCV infection progress to chronic hepatitis. Chronic viral hepatitis is a result of prolonged, ongoing, slow inflammatory injury to hepatocytes accompanied by regeneration and fibrosis. It may ultimately, though in a small proportion, culminate into liver cirrhosis which is characterized by ascites, variceal bleeding, hepatic encephalopathy, hepatorenal syndrome and occasionally hepatocellular carcinoma. Acute liver failure, which is a result of sudden massive loss of hepatocyte function, is characterized by coagulopathy and altered sensorium and will be dealt elsewhere separately.

Atypical Features of Acute Hepatitis A

Cholestatic Hepatitis

This clinical form, though relatively uncommon, is seen in children recovering from acute HAV. The patients continue to have deep icterus during the convalescent phase. This is accompanied by intense pruritus, which may impair sleep, work, and quality of life.

Table 2 Salient features of three phases of viral hepatitis

Symptoms	Signs	Laboratory
Prodromal phase		
<ul style="list-style-type: none"> • Precedes jaundice • Anorexia, aversion of taste and smell (80–90%) • Nausea, vomiting • Abdominal discomfort, right upper quadrant pain • Low grade fever • Malaise, myalgia, fatigue, arthralgia • Headache, photophobia, neck rigidity (occasional) • Lasts for 5–7 days 	<ul style="list-style-type: none"> • No icterus • Mild, soft hepatomegaly • Right upper quadrant mild tenderness • Serum sickness-like features: arthritis, skin rash (particularly acute hepatitis B) • Occasional mild, soft, non-tender splenomegaly 	<ul style="list-style-type: none"> • Normal bilirubin • Marked elevation of ALT and AST (usually >10-fold, up to 100 times, peak in prodromal or early icteric phase) • Slight elevation of alkaline phosphatase • Normal or mildly deranged prothrombin time in absence of acute liver failure
Icteric phase		
<ul style="list-style-type: none"> • Yellow discoloration of eyes and urine • Improvement of appetite and other prodromal symptoms • Feeling well and active • In some, mild itching • Lasts for up to 6 weeks 	<ul style="list-style-type: none"> • Jaundice of variable severity • Mild, soft hepatomegaly • Occasional mild, soft, non-tender splenomegaly • Scratch marks, if itching present 	<ul style="list-style-type: none"> • High serum bilirubin, predominantly conjugated • Moderately elevated ALT and AST
Convalescent phase		
<ul style="list-style-type: none"> • Almost complete recovery of symptoms • Mild icterus and fatigue may persist for a few weeks 	<ul style="list-style-type: none"> • Icterus—moderate to mild; gradually improving • Normalization of urine color • Regression of organomegaly 	<ul style="list-style-type: none"> • Near normal bilirubin • Normal or slightly elevated ALT and AST • Normal alkaline phosphatase

These symptoms may continue for a few weeks to months, with spontaneous and complete recovery. Patients need counseling and antipruritic measures while awaiting natural recovery.

Relapsing Hepatitis

Up to 10% of children with hepatitis A may have a biphasic illness, which probably represents endogenous reinfection due to prolonged enterohepatic circulation of HAV. It is characterized by second attack of hepatitis 4–8 weeks following the initial recovery. The second attack is usually in the form of either subclinical elevation of transaminases or mildly symptomatic disease; however, sometimes, a full blown attack of hepatitis may occur. Rarely, multiple relapses, with each episode associated with viral excretion in stool, may occur. Relapsing hepatitis finally recovers fully.

Progression to Autoimmune Hepatitis

Rarely, patients recovering from HAV infections have been shown to develop autoimmune hepatitis. Its occurrence possibly depends on individual susceptibility for autoimmune hepatitis, which is merely precipitated by HAV infection.

Extrahepatic Manifestations

Occasionally, HAV infection may be associated with involvement of other body organ systems, such as kidney (proteinuria, glomerulonephritis, nephrotic syndrome, acute renal failure), nervous system (aseptic meningitis, encephalitis, seizure, myelitis, Guillain-Barré syndrome, mononeuritis, mononeuritis multiplex), pancreatobiliary organs (acalculous cholecystitis, acute pancreatitis), and hematological system (autoimmune hemolytic anemia, pure red cell aplasia, aplastic anemia). These manifestations have also been reported in persons with infection due to other hepatotropic viruses, though with a somewhat lower frequency.

DIFFERENTIAL DIAGNOSIS

Diagnosis in a child presenting with fever, systemic symptoms, and jaundice in summer or rainy season may at times be confused with other water-borne or vector-borne infections with similar presentation. Occasionally, in a child, AVH needs to be

distinguished from acute exacerbation of a pre-existing chronic liver disease. In a child with suspected AVH, an alternative diagnosis should be considered, if the child (1) does not show expected recovery; (2) worsens in the absence of features indicating acute liver failure; (3) continues to have fever after appearance of jaundice; or, (4) has atypical clinical features. **Table 3** summarizes the clinical and laboratory features that help to differentiate AVH from other diseases.

Approach to Diagnosis

Diagnostic algorithm for approaching a child with suspected AVH is summarized in **Flow chart 1**. In every child with AVH, one should be on the lookout for clinical and biochemical features of ALF, which needs special care and management.

MANAGEMENT

Acute viral hepatitis needs no specific therapy; rather only supportive measures and careful monitoring are needed.

Supportive Therapy

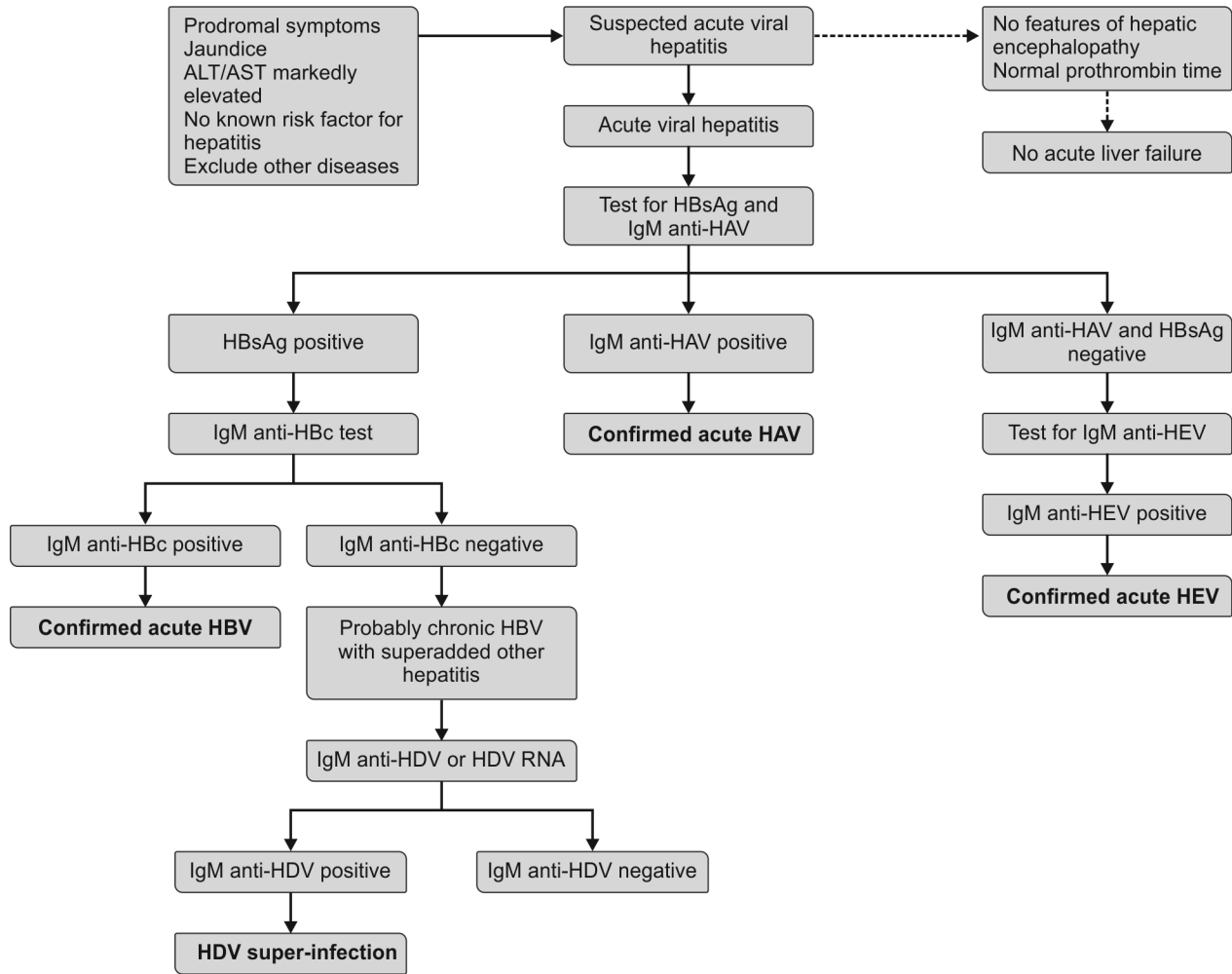
Child can continue his daily routine with light physical activity till symptoms subside. There is no role for strict bed rest. Hygienic measures help prevent spread to other family members. Use of boiled water after the onset of AVH is of no use. Antipyretic, antiemetic and mild analgesic drugs may be used for symptomatic relief. Vitamins (particularly vitamin K), appetizers, antibiotics, hepatoprotective medications (e.g., Liv-52, ursodeoxycholic acid), etc. have no role. Dietary restrictions (of fat, milk, turmeric, pickles, spices, etc.) offer no benefit and may in fact adversely impact nutrition.

Counseling

Parents should be counseled about (1) benign nature of illness, (2) high likelihood of complete natural recovery, (3) avoidance of restrictions on physical activity and diet, and (4) lack of role for drugs including antiviral agents. For hepatitis B and C, need to follow-up till viral clearance should be emphasized, in view of possibility of chronicity.

Table 3 Differential diagnosis of acute viral hepatitis

Differential diagnosis	Symptoms	Signs	Investigations
Malaria	Moderate to high grade intermittent fever with chills and rigor	Pallor; moderate splenomegaly	Anemia; mild unconjugated hyperbilirubinemia; reticulocytosis; intravascular hemolysis; malaria parasite positive; relatively moderate ALT/AST elevation
Dengue hepatitis	Severe body ache	Petechial rash	Thrombocytopenia; dengue antibody or antigen (NS1) test positive; mild to moderately elevated bilirubin, ALT, AST; ascites or pleural effusion
Enteric hepatitis	Continuous high-grade fever	Toxic look; poor general condition; moderate splenomegaly	Leukopenia; blood culture or Widal test positive
Acute exacerbation of chronic liver disease	History of factors predisposing to chronic liver disease; symptoms of chronic liver disease (ascites, gastrointestinal bleed, encephalopathy)	Ascites; firm splenomegaly; dilated abdominal veins; encephalopathy; stigmata of chronic liver disease	Pancytopenia; low albumin; prolonged prothrombin time; ultrasound features of cirrhosis; gastroesophageal varices on endoscopy
Liver abscess	Marked right upper quadrant pain; breathing difficulty	Right upper quadrant or right intercostal tenderness; tender hepatomegaly; right-sided pleural effusion	Leukocytosis; mildly elevated bilirubin, no or mild ALT/AST elevation; ultrasound abdomen showing liver abscess
Cholangitis	Moderate to high grade intermittent fever with chills; biliary pain	Firm, moderate hepatomegaly; features of biliary disease, e.g., palpable gallbladder	Marked conjugated hyperbilirubinemia; mildly elevated ALT, AST; marked elevation of alkaline phosphatase and γ -glutamyl transferase; ultrasound abdomen showing biliary radicle dilatation

Flow chart 1 Algorithm to approach a child with suspected viral hepatitis

Monitoring

A child with AVH needs to be monitored for possible complications particularly ALF. Child could be monitored for age appropriate subtle signs of hepatic encephalopathy such as flapping tremors, altered sleep patterns, excessive irritability and inconsolable cry. The only laboratory test we need to monitor is prothrombin time, if it was abnormal earlier or there is any clinical evidence of deterioration. Prolongation of prothrombin time is the most reliable and early marker of worsening liver function or impending liver failure. Repeated measurement of no other liver function tests, including bilirubin and serum transaminases levels, are needed to monitor a child with acute hepatitis.

PROGNOSIS

Barring occasional cases that develop ALF, most children with AVH have spontaneous and complete recovery without any sequelae. Children with ALF have high risk of mortality in lack of intensive care setting and liver transplantation facility. Akin to AVH, children survived of ALF will not be left with any sequelae or persistent liver damage. As discussed earlier, some children with acute HBV and majority of those with HCV infection will develop chronic hepatitis. Risk of developing chronic HBV is primarily determined by the age of infection acquisition, with risk being much higher when the infection occurs in infancy (> 90%) or early childhood (> 20% if age < 5 years) and below 5% when it occurs in adulthood. Over the decades, a small proportion of chronic infection with HBV or HCV

may culminate in liver cirrhosis. Liver cirrhosis is associated with impaired quality of life, life threatening morbidities and high risk of death.

PREVENTION

Viral hepatitis could be prevented by changing our different practices, vaccination or immunoglobulin administration (**Table 4**). Effective vaccines are available against HAV and HBV. HDV infection can be prevented by preventing HBV infection. Vaccines and immunoglobulin will be dealt elsewhere in details.

IN A NUTSHELL

1. Five hepatotropic viruses, A to E, cause majority of acute viral hepatitis episodes.
2. Hepatitis A virus followed by hepatitis B virus are the most common viral agent for hepatitis in children in India.
3. Clinical course of acute viral hepatitis due to various hepatotropic viruses is indistinguishable.
4. Most patients with viral hepatitis improve spontaneously.
5. In patients with acute viral hepatitis, degree of ALT/AST elevation has no relation with disease severity or outcome.
6. Only a few children with acute viral hepatitis progress to liver failure.
7. HBV or HCV infection may progress to chronic hepatitis.

Table 4 Summary of preventive measures applicable for children against hepatitis viruses, A to E

<i>Preventive measures</i>	<i>HAV</i>	<i>HBV</i>	<i>HCV</i>	<i>HDV</i>	<i>HEV</i>
Water and food hygiene, and sanitation measures	Yes				Yes
Safe injection practices		Yes	Yes	Yes	
Safe blood/blood product transfusion		Yes	Yes	Yes	
Antenatal screening		Yes			
Vaccination	Yes	Yes		Yes, hepatitis B vaccine	
Immunoglobulin	Yes	Yes			

Abbreviations: HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus; HEV, hepatitis E virus

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Chapter 31.10

Rabies

Jaydeep Choudhury

Rabies is acute viral encephalitis transmitted by exposure to rabid animals. It is principally a zoonotic disease. It is considered as one of the most dreaded diseases. The term *exposure* to rabies means bite, scratch or lick directly on mucous membrane or on broken skin and also aerosol infection by infected animals. Organ transplant can also transmit this disease. When infection sets in, rabies is invariably fatal. On the other hand rabies is a vaccine preventable disease, especially when vaccination is combined with immunoglobulin therapy.

EPIDEMIOLOGY

Rabies is endemic in many of Asian and African countries. India is a high endemic country for rabies. Only the islands of Andaman and Nicobar in east and Lakshadweep islands are rabies free. According to latest WHO estimates, about 50,000 human deaths due to rabies are reported every year in the world. It is estimated that about 20,000 human rabies deaths occur in India every year. The annual animal bite incidence is 17.4 per 1000 population. The biting animal mainly responsible for human rabies death was dog. It is estimated that 96.3% of all reservoirs of rabies are dogs. Majority were stray dogs (75.3%) followed by pets (11.1%), wild (3.5%) and otherwise or unknown (10.2%).

VIRUS

Rabies virus is a single stranded RNA virus belonging to the genus *Lyssavirus* of the family *Rhabdoviridae*. The rabies virus is a typical bullet shaped virus measuring usually 100–300 nm in length depending on strain and 75 nm in breadth. Rabies virus is a neurotropic virus. It has phospholipid envelop which has glycoprotein spikes on surface. The surface projection of glycoprotein, which is related in attachment of virus to susceptible cells, also carries the antigen which elicits the production of neutralizing antibody when isolated in animals and hence affords protection against the disease. The rabies virus is resistant to cold temperature, dryness and decays but is rapidly inactivated by the action of oxidizing agents, solvents, quaternary ammonium compounds, soap and detergent as presence of lipid in the outer coat of rabies virus particle makes it relatively easy to disrupt them simply by addition of a lipid solvent.

As rabies virus is highly neurotropic virus, it can infect any warm blooded animal including man. There seems to be a variation in the susceptibility of different animal species to the virus infection. Wild animals like fox, jackal, mongoose, etc. are highly susceptible compared to dogs, cats and domestic animals.

RESERVOIR

Two cycles of rabies exist, sylvatic and urban. Foxes, raccoons, skunks, jackals, mongooses, bats, etc., maintain the sylvatic cycle. Dogs, cats, cattle, horses, sheep, pigs, etc., maintain the urban cycle. The exposures are reported frequently by dogs and cats, sometimes by monkeys, horses, sheep, cows, buffaloes, donkeys, pigs, occasionally by elephants, camels, foxes, mongooses, jackals, bears, which may lead to rabies. But rabies deaths due to small rodents have not been reported.

TRANSMISSION

The followings are the modes of transmission of rabies infection: (1) bite, (2) scratch, (3) lick on damaged skin and intact mucous membrane by rabid animals, (4) organ transplant—cornea transplant mainly and (5) aerosol spread in bat infested caves. The commonest mode of transmission of virus to human population is the bite from infected dogs. Rabies virus can not penetrate intact skin. An old injury on the skin can also allow entry of virus. So contamination of broken skin with saliva of rabid animal by simple licking can be dangerous. Scratches by rabid animals are also considered another mode of transmission, which allow virus entry. Rabies virus can penetrate intact mucous membrane. Drinking of raw milk of infected cow, buffalo or goat is such an example. Contact of saliva of rabid animals in anal region or mouth cavity, i.e., moist mucous surfaces is also considered to be dangerous.

PATHOGENESIS

After entering the human body, the virus replicates in muscles around the wound. Then it gains access to nerve endings and starts traveling at the rate of 3 mm/hour towards central nervous system. The virus ascends passively in the axoplasm of the nerves and reach dorsal root ganglion where they again replicate and reaches the anterior horn cells of spinal cord and then spreads to neurons of the spinal cord. Once CNS is involved there is rapid and extensive replication of virus in brain and spinal cord. Initially some areas like hippocampus, hypothalamus and limbic system are predominantly involved.

CLINICAL FEATURES

Average incubation period varies between 3 weeks and 3 months. It is highly variable, may be as short as 4 days to as long as 3 years. The size of inoculum of virus and the bites in head and neck region due to proximity to brain, in hands due to excess innervations may have some significance in the early causation of the disease.

There are 2 distinct clinical forms, furious rabies and dumb rabies. *Furious type* is seen in 80% cases, characterized by symptoms related to spasms of gullet, namely hydrophobia, aerophobia and others aggressiveness leading to coma and death in 3–5 days after onset of symptoms. *Dumb* or *paralytic type* is seen in 20% cases characterized by progressive onset of ascending paralysis. The order of involvement is lower limbs, abdominal muscles, upper limb and thoracic muscles, followed by coma, respiratory failure and death which is delayed and patient may live little longer, sometimes as long as a month.

DIAGNOSIS

Diagnosis of rabies is mostly clinical as 80% of cases present with hydrophobia, aerophobia and aggressiveness. Antemortem diagnosis can be attempted by detection of viral antigen in saliva or CSF, corneal smear immunofluorescent examination, and detection of viral nucleic acid in saliva and CSF by reverse transcriptase (RT)-PCR analysis. Postmortem diagnosis by demonstration of Negri bodies within the brain sample is 100% pathognomonic of rabies. Serological assays to measure the presence of antibody to rabies virus have been used for decades and represent an extremely useful tool for diagnosis, epidemiology and measurement of an immunological response after vaccination. Conducting rabies serological testing in an appropriate and correct manner is a complicated procedure.

TREATMENT

Nursing care, symptomatic therapy with sedatives, analgesics, proper hydration and intensive therapy are some main steps of the treatment of rabies patients. Parenteral diazepam, lorazepam or midazolam can be given to reduce psychomotor excitation. Better result can be obtained if it is administered along with antihistaminic and analgesics. At the same time patient has to be protected from external stimuli such as draughts, noise or bright light. Dehydration is severe and dramatic in all cases due to aversion of drinking water, excessive sweating and salivation, which demands a special care for the water salt balance. Massive intravenous infusions are required in all the patients. Prednisolone and mannitol may be administered to the patients with high intracranial pressure. Respiratory and cardiac support may be given to alleviate the sufferings and ensure peaceful death to the victim. There are a few sporadic reports of recovering from rabies following such treatment.

Individuals who Come in Contact with Rabies Patients

Persons who come in contact with rabies patients or who nurse those patients or who handle saliva or secretions of rabies patients, must take a full course of anti-rabies vaccine. They must be very cautious that they are not accidentally bitten or the saliva of the patient does not come in contact with any fresh cut, abrasions or mucous membranes of their body.

PREVENTION

Clinical categorization of rabies exposure as per WHO recommendation is a useful tool to treat an animal exposure case (**Table 1**). A transdermal wound in any place of the body or a mucous membrane contamination with saliva is to be dealt most seriously. Majority of wounds and exposures are of category III type. The following protocol is effective for prevention of rabies in a fresh exposed case irrespective of the fact of extension of exposure or the animal concerned. The steps are described below.

Step 1 Local washing of the wound thoroughly with soap and water. This step invariably reduces the virus load of the wound physically (running water) and inactivating the remaining particles of virus chemically (soap or detergent).

Step 2 Application of 70% alcohol, tincture of iodine, povidone iodine, or any other suitable disinfectant after removing all traces of soap, alcohol and other disinfectants. This leads to further

inactivation of remaining virus by chemical disruption. The animal bite wounds should not to be covered. Suturing of the wound should be avoided. When the suturing is unavoidable for the purpose of hemostasis, it must be ensured that immunoglobulins have been administered in the wound(s) prior to suturing.

Step 3 Proper infiltration of the wound(s) with rabies immunoglobulins (RIG) of human (HRIG) or equine (ERIG) origin. The dose of HRIG is 20 IU/kg of body weight and that of ERIG is 40 IU/kg of body weight. Skin test for sensitivity is not essential either for HRIG or ERIG. RIGs are specific rabies virus neutralizing antibodies that immediately neutralize rabies virus on contact. RIG gives a coating to the virus so that it cannot enter the nerve endings resulting reduction or total obliteration of inoculated virus.

The RIG should be infiltrated thoroughly into and around the wound. The remaining portion of the calculated amount of the RIG if any is to be injected in the deltoid region in older children and adults or anterolateral surface of thigh in newborns, infants and smaller children away from the site of vaccine administration to prevent onsite neutralization of vaccine antigen. If the administration of the RIG is delayed initially it can be administered up to 7th day after the 1st dose of vaccine, i.e., along with 3rd dose of vaccine, but in a separate site.

Step 4 Vaccination against rabies. It is advisable to administer a potent modern tissue culture rabies vaccine (MTCV) following an approved schedule which results in production of systemic antibodies against rabies after a lag period of 7–14 days from the 1st dose of ARV.

Antirabies Vaccines

The use of nerve tissue vaccines is now abandoned in India after the Supreme Court ruling. *Duck embryo vaccine* is presently available as purified duck embryo cell vaccine (PDEV). The purified duck embryo cell vaccine is claimed to be as immunogenic as the modern tissue culture vaccines. *Modern tissue culture vaccines* are now considered as the gold standard in rabies prevention. These vaccines are safe, potent and convenient to use. Three types of MTCV are available in India. Those are: (1) purified chick embryo cell vaccine (PCEC), (2) human diploid cell vaccine (HDCV) and (3) purified Vero cell vaccine (PVRV).

Schedules of Vaccinations Against Rabies

Intramuscular Regimens

Essen protocol (Table 2)—The WHO standard schedule commonly known as *Essen Protocol* comprises 5 IM injections on days 0, 3,

Table 1 WHO recommendations for management of animal bites

Category	Type of contact with suspected or confirmed domestic or wild animals* or animal unavailable for observation	Recommended treatment
I	Touching or feeding of animals, licks on intact skin	None, if reliable case history is available
II	Nibbling of uncovered skin, minor scratches or abrasions without bleeding, licks on broken skin	Administer vaccine immediately.** Stop treatment if animal remains healthy throughout an observation period of 10 days,*** Or, if the animal is euthanized and found to be negative for rabies by appropriate laboratory technique
III	Single or multiple transdermal bites or scratches, contamination of mucous membrane with saliva (i.e., licks)	Administer rabies immunoglobulins and vaccine immediately,** Stop treatment if animal remains healthy throughout an observation period of 10 days,*** Or, if the animal is euthanized and found to be negative for rabies by appropriate laboratory techniques.

*Exposure to rabbits, rodents and hares seldom if ever requires specific antirabies treatment

**If an apparently healthy dog or cat in or from a low risk area is placed under observation it may be justified to delay specific treatment

***This observation applies only to dogs and cats.

Table 2 Essen protocol (IM Schedule) for postexposure prophylaxis of rabies

	Days of vaccination					
	Day 0	Day 3	Day 7	Day 14	Day 28	Day 90
No. of doses	1 IM dose	1 IM dose	1 IM dose	1 IM dose	1 IM dose	Dose optional

7, 14, 28 or 30. The 6th dose on day 90 is optional which is administered in selected cases like in extremes of ages, with debility and protein energy malnutrition, in immunocompromised patients, with neoplastic diseases, undergoing antimalarial treatment, suffering from viral hepatitis, presently taking steroid containing drugs for long time, etc. This schedule is practiced in our country as we are in the highest endemic zone of rabies.

Intradermal Schedules

2-2-2-0-1-1 ID schedule (Thai Red Cross ID schedule or TRC-ID schedule) (Table 3)—Two ID doses given on day 0, day 3 and day 7 on two deltoids, one ID dose on one site of deltoid on day 28 and 90. No dose is given on day 14. One ID dose is 1/5th of quantity of IM dose depending on vaccine though 0.1 mL of purified chick embryo cell vaccine is also used successfully in community practice. But the ID schedule is recommended only for the centers where at least 10 antirabies vaccines are given in a day, otherwise there will be wastage of vaccine.

Pre-exposure Schedule

Pre-exposure vaccination Rabies is the infectious disease where active immunization is administered after the exposure. This group of vaccination is termed as postexposure vaccination. But it is possible to administer pre-exposure vaccination to protect individuals at risk of rabies even before the exposure has occurred, namely, to the veterinary doctors, municipal workers, postmen and women, taxidermists, laboratory and research workers in the field of rabies, dog handlers, etc.

Intramuscular (IM) pre-exposure schedule Three IM doses are to be given on days 0, 7 and 21 or 28 intramuscularly. A booster dose is needed after 1 year of 1st dose and then booster doses every 3 yearly to keep an effective antibody titer against rabies.

Intradermal (ID) pre-exposure schedule Now a days 0.1 mL ID of MTCV doses are also accepted scientifically as pre-exposure doses on days 0, 7, 28 then 0.1 mL ID dose of MTCV every year.

Table 3 Thai Red Cross-intradermal (ID) Schedule (2-2-2-0-1-1) for postexposure prophylaxis of rabies

	Days of vaccination					
	Day 0	Day 3	Day 7	Day 14	Day 28	Day 90
No. of doses	2 ID doses in 2 separate sites	2 ID doses in 2 separate sites	2 ID doses in 2 separate sites	No dose	1 ID dose	1 ID dose

1 ID dose = 1/5 of IM dose both in PBRV and PCEC
Only for community practice 0.1 mL of PCEC per dose is also used.

Adverse Reactions of MTCV

The tissue culture rabies vaccines are safe and well tolerated. Mild local effects such as pain, redness and swelling may be observed in 10–20% of the recipients. Systemic manifestations such as fever, malaise, headache, abdominal pain may be seen transiently in a few vaccines and can be minimized by the use of anti-inflammatory drugs. Very rarely immune complex reactions and neurological illness resembling Guillain-Barré syndrome have been reported in temporary association with HDCV.

Revaccination for Repeat Exposures in Previously Vaccinated Persons

There is no need of RIG administration during the repeat exposure when there is past history of complete pre- or postexposure vaccination. The recommendation is to repeat vaccinations with 2 booster doses, one on day 0 and other on day 3 if there is history of complete postexposure or pre-exposure treatment previously within 3 years. Any exposure after 3–5 years of vaccination, are treated with complete postexposure vaccination excluding RIG administration in our country.

IN A NUTSHELL

1. India is a high endemic country for rabies.
2. Modes of transmission are bite, scratch, lick on damaged skin, intact mucous membrane and organ transplant. After entering the human body, the virus replicates in muscles around the wound and then it gains access to nerve endings and starts traveling.
3. Two distinct clinical forms exist—furious rabies and dumb rabies. The former is seen in 80% cases, characterized by hydrophobia, aerophobia and aggressiveness.
4. Rabies is almost 100% fatal but 100% preventable.
5. Local washing of the wound thoroughly with soap and water reduces the virus load.
6. Proper infiltration of the wound(s) with rabies immunoglobulins should be done in all WHO category III exposure.
7. Modern tissue culture vaccines are effective in postexposure and pre-exposure rabies prevention.

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Chapter 31.11

Japanese Encephalitis

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Japanese encephalitis (JE) is the single largest cause of viral encephalitis in the world today with a reported 45,000 cases, 10,000 deaths and 15,000 survivors left with disability annually. This too is very likely an underestimate due to lack of diagnostic facilities and surveillance systems in regions affected. The disease is endemic in several states in India with frequent outbreaks in eastern UP, Bihar, West Bengal, Assam and Andhra Pradesh with large number of morbidity and mortality among children under 15 years of age.

HISTORY AND DISTRIBUTION

Japanese encephalitis is mainly an Asian disease. Summer epidemics of encephalitis occurred in Japan as far back as the 1870s. In 1935 the virus was isolated from a fatal human case. Since that time it spread to most of South East Asia and its presence is being increasingly recognized in this region and also the Western Pacific islands and northern Australia. Presently JE is reported from 25 countries—Australia (Torres Strait Islands), Bangladesh, Bhutan, Brunei, Burma, Cambodia, China, India, Indonesia, Japan, North Korea, South Korea, Laos, Mongolia, Nepal, Pakistan, Papua New Guinea, Philippines, Russia, Singapore, Sri Lanka, Taiwan, Thailand, Timor-Leste, Vietnam, and western Pacific islands. In India, the disease was first recognized in the 1950s from Vellore. The first large epidemic occurred in West Bengal (Bankura district) in 1973. Since then it is endemic in southern and eastern states with monsoon and post monsoon outbreaks. It is also showing a westward trend and presently human cases are reported from all states except Dadra, Daman, Diu, Gujarat, Himachal Pradesh, Jammu and Kashmir, Lakshadweep, Meghalaya, Nagar Haveli, Punjab, Rajasthan and Sikkim.

THE VIRUS

The Japanese encephalitis virus (JEV) is a single stranded positive sense neurotropic RNA virus belonging to the *Flavivirus* genus, family *Flaviviridae*. It is closely related to other flaviviruses like dengue, chikungunya, St Louis encephalitis, Murray Valley encephalitis, tick borne encephalitis and yellow fever. In fact there is cross reactivity between flaviviruses.

The JE virion RNA is wrapped in a nucleocapsid and surrounded by a glycoprotein containing envelope. There are 3 structural proteins—pre membrane (PrM), core (C) and envelop (E), and 7 nonstructural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, NS5). The E protein is the largest structural protein related to neurovirulence and is the main target for humoral immune response. There are 5 genotypes I to V, based on the nucleotide sequence of the envelop (e) gene. Genotype I and III were found mainly in northern temperate *epidemic* regions and genotypes II and IV were found in southern *endemic* regions. Japanese encephalitis virus genotype V was first reported from Malaysia in 1952 (Muar strain) and re-emerged after a 57-year hiatus in Asia (China) in 2009. Until 2007, all known Indian JEV strains belonged to G III. However, recently, G I has been isolated from the Gorakhpur region, India.

NATURAL CYCLE

Japanese encephalitis is a zoonosis and the virus circulates in nature between the vector and vertebrate hosts. The main vector all over Asia is the *Culex tritaeniorhynchus*—a zoophilic rice field breeding

mosquito. Other vectors like *C. vishnui*, *C. pseudovishnui* and some anopheles mosquitos are also known. The main vertebrate hosts all over Asia are the pig and birds of the family Ardeidae. These hosts have significant viremia and therefore are able to harbor, amplify and transmit the virus without developing illness, although the cycle may get aborted in pigs. Man is only an incidental dead-end host with very short viremia which does not allow further transmission. Cattle do not have significant viremia and do not develop disease but can support a large population of mosquitos.

EPIDEMIOLOGY

This is explained by the natural cycle as the disease occurs in poor rural folk in rice growing areas where pig rearing is common. Japanese encephalitis tends to occur in epidemics and outbreaks which coincide with peak mosquito activity. Two main patterns of occurrence are seen. In *northern* regions it occurs as summer epidemics while in southern regions it is endemic with monsoon/postmonsoon peaks. It is primarily a disease of children of 5–15 years age and young adults, incidence being 1–10 per 10,000 in affected areas. When a new nonimmune population is involved, adults are also commonly affected. There is a scattered pattern of incidence with only 1–2 cases occurring per village and some villages are completely spared. A study of laboratory proven cases of JE in children hospitalized during the 2005 epidemic in Uttar Pradesh, India revealed that children below 2 years of age were not affected, boys accounted for three fourths of the cases and almost all patients hailed from rural areas.

PATHOGENESIS

Factors which determine the course of infection include agent factors—titer of inoculum, strain virulence and route of entry, and host factors—age, genetic makeup, immunity and general health. The JEV E protein plays a major role in virulence phenotype; even single amino acid substitutions may cause loss of neuroinvasiveness.

Japanese encephalitis virus enters the body through a mosquito bite, multiplies within host leukocytes (probably T lymphocytes) and is carried to the central nervous system (CNS). The virus particles bind to the endothelial surface of the brain blood vessels and are internalized by endocytosis. Damage in flaviviral encephalitis appears to result both from direct virally mediated damage as well as host inflammatory response. Microglial cells undergo uncontrolled overactivation, releasing proinflammatory cytokines. This promotes massive leukocyte migration and infiltration in the brain. Recently, apoptosis has been shown in vitro in different cell lines for various arboviruses. IgM antibody and T lymphocytes play a major role in the clearance of the virus after infection. Pre-existing ant flaviviral antibodies may protect against severe disease.

PATHOLOGY

The brain bears the brunt of the infection. There is swelling and intense congestion of the gray matter with confluent areas of hemorrhage. A characteristic but not pathognomonic finding is focal punched out areas of necrosis in the gray matter. Infiltration of meninges and perivascular areas with mononuclear cells is seen. The cerebral cortex shows microglial infiltration with circumvascular necrotic zones with total loss of neurons, whereas the white matter is fairly well-preserved.

CLINICAL FEATURES

Japanese encephalitis virus infection can be asymptomatic or can cause an acute undifferentiated febrile illness or meningo-

cephalitis. Like most other viral meningoencephalitides, the course of JE can be divided into three stages—(1) *prodromal stage* with nonspecific fever, headache, vomiting, diarrhea, etc., lasting from a few hours to days; (2) *acute encephalitic stage* with continuing fever, convulsions, coma and signs of raised intracranial tension lasting 7–10 days and; (3) *convalescent stage* with gradual improvement over weeks to months. In severe cases signs of raised intracranial tension, hyperventilation, shock and death may occur in quick succession. A study on 77 laboratory confirmed cases showed mean prodromal stage of 2.6 (SD = 2.23) days, convulsions in 98.7%, mean Glasgow Coma Scale on admission of 7.4 (SD = 2.7), focal neurological deficits in 45.4%, extrapyramidal signs in 31.1%, hyperventilation in 26%, gastric hemorrhage in 54.5% and early mortality of 34%. A study to identify clinical features of JE to differentiate it from other similarly presenting illnesses revealed that hyperventilation in the acute stage and extrapyramidal features were significant independent predictors of the diagnosis.

Sequel A follow-up study on 55 laboratory confirmed cases showed that major sequelae (frank intellectual disability, frank motor deficits or epilepsy) were present in 45.4% and another 25% had minor sequelae (behavioral disturbances, scholastic backwardness or subtle neurological signs) after more than 1 year. Less than 30% were normal. JE can also cause lower motor neuron paralysis possibly due to myelitis.

DIAGNOSIS

A neutrophil leukocytosis is seen in the peripheral blood in most cases. Cerebrospinal fluid (CSF) examination may reveal a normal cell count or mild to moderate pleocytosis with elevated protein but normal sugar. During the JE epidemic of 2005, half the children seen in Lucknow had normal CSF and in the remainder there was a mild pleocytosis. Maximum CSF cell count was 300/cu mm and only 12.3% patients had counts beyond 100/cu mm. Electrophysiological studies revealed EEG abnormalities in 80%, in the form of nonspecific θ - δ slowing, α coma, periodic lateralized epileptiform discharges and other epileptiform discharges or burst suppression. Muscle evoked potentials (MEP) were abnormal in 70%, correlating with weakness and poor 3 month outcome. Electromyograms and somatosensory evoked potentials (SSEP) also revealed abnormalities in a small proportion of patients.

Microbiological Diagnosis

For IgM detection, blood and CSF should be collected at least 5 days after the onset of illness. Serum, blood and CSF should be stored at 4–8°C and transported in ice to the laboratory. If testing is likely to be delayed beyond 1 week the sample can be stored at –20°C. However, repeated freezing and thawing is undesirable as it results in denaturation of antibody. Time since onset of illness should be mentioned on the sample. For isolation of virus and detection of viral genome by PCR, blood and CSF samples should be collected within 4 days after the onset of illness.

Earlier the diagnosis was confirmed by viral isolation from CSF or brain by intracerebral inoculation in infant mice followed by the quick complement fixation test. Hemagglutination inhibition test is done in paired sera taken 10–14 days apart but cross reactions occur with other flaviviruses and parallel testing needs to be done. The most widely used test is detection of JEV specific IgM by ELISA. The test is usually positive in CSF and serum by about 7 days of illness and has 95% sensitivity and specificity in CSF by 10 days of illness. If sample taken early in the illness is negative the test should be repeated around this time.

Viral isolation and detection of JEV genome is possible from CSF or brain early in the illness but the yield is low and cannot be used to rule out the diagnosis.

Radiological Features

Typical changes involve bilateral thalami, basal ganglia, putamen, pons, cerebellum and spinal cord. Magnetic resonance imaging (MRI) is more sensitive. In one study, computed tomographic scans (Fig. 1) were abnormal in 55% while MRI scans were abnormal in all. Association with neurocysticercosis is seen.



Figure 1 Computed tomographic scan image of a patient of Japanese encephalitis showing changes in thalamus and basal ganglia

DIFFERENTIAL DIAGNOSIS

A wide variety of disorders can mimic JE. These include other viral encephalitides—arboviruses, enteroviruses, Herpes group, myxoviruses, paramyxoviruses, adenoviruses, parvoviruses and rhabdoviruses, CNS invasion by nonviral agents, noninfectious inflammation—acute disseminated encephalomyelitis, antibody associated encephalitis, infectious encephalopathies (cerebral malaria, shigella encephalopathy, dengue encephalopathy, enteric encephalopathy and sepsis associated encephalopathy) and functional and structural causes of coma if associated with fever due to some other cause.

SURVEILLANCE

In 2006, recognizing the public health proportions of Japanese encephalitis in endemic regions, WHO coined the term acute encephalitis syndrome (AES) for surveillance purposes. Clinically, AES is defined as “a person of any age, at any time of year with acute onset of fever and at least one of: (1) change in mental status (including symptoms such as confusion, disorientation, coma, or inability to talk); (2) new onset of seizures (excluding simple febrile seizures). Other early clinical findings may include an increase in irritability, somnolence or abnormal behavior greater than that seen with usual febrile illness” WHO case classification of AES is depicted in Box 1.

The large majority of JE infections are asymptomatic. Therefore, in areas that are highly endemic for JE, it is possible to have AES due to a cause other than JE virus and have JE virus-specific IgM antibody present in serum. To avoid implicating asymptomatic JE as the cause of other AES illnesses, sterile collection and testing of a CSF sample from all persons with AES are recommended when feasible. During periods of epidemic transmission of JE virus, laboratory confirmation of every case may not be necessary.

BOX 1 WHO case classification of acute encephalitic syndrome (AES)

AES: a case that meets the clinical case definition of AES above. AES cases should be classified in one of the following 4 ways:

Laboratory confirmed JE: An AES case that has been laboratory confirmed as JE.

Probable JE: An AES case that occurs in close geographical and temporal relationship to a laboratory confirmed case of JE, in the context of an outbreak.

AES—other agent: An AES case in which diagnostic testing is performed and an etiologic agent other than JE virus is identified.

AES—unknown: An AES case in which no diagnostic testing is performed or in which testing was performed but no etiologic agent was identified or in which test results were indeterminate.

WHO Recommendations for JE Surveillance

According to WHO, “When feasible, surveillance should be performed within the context of integrated disease surveillance and linked with similar surveillance activities such as those for acute flaccid paralysis or meningitis. JE surveillance should be conducted year round. Two types of surveillance are recommended:

1. *In all Asian countries* Comprehensive syndromic surveillance for acute encephalitis syndrome (AES) with aggregate reporting is recommended. In sentinel hospitals, surveillance should be case based with specimens collected for laboratory confirmation. The number of sentinel hospitals should be gradually increased if feasible.
2. *In Asian countries where a high level of JE control has been achieved* surveillance should be case based throughout the country and include laboratory confirmation of all suspected cases.

Regardless of the type of surveillance, reporting should be weekly or monthly and include *zero-reporting* (i.e., no blanks should be left in the reporting forms, a zero should be indicated when there are no cases detected). Outbreak investigations should be initiated if there is a sudden increase in cases or if cases reported are different from historical information, in terms of season, geographical area, age group, or case fatality.”

TREATMENT

Treatment of JE is essentially supportive. A severe case should be managed in an intensive care setting with careful monitoring,

maintenance of homeostasis and good nursing care. Antipyretics and anticonvulsants should be given as necessary. Measures to reduce intracranial tension such as mannitol infusions, glycerol, acetazolamide and positive pressure ventilation to maintain arterial carbon dioxide between 25 mm Hg and 30 mm Hg may be required. No specific antiviral treatment has shown benefit in randomized controlled trials. A study of interferon α in Vietnamese children failed to show benefit as did another trial of oral/nasogastric ribavirin in Indian children. Steroids also have not shown benefit. Recently the tetracycline drug minocycline has been shown to accord complete protection against JE in mouse model.

PREVENTION

Control of JE can be directed to control of the vector through insecticide spray, larvicides, bed nets, repellants, and in the long-term, better water management. Measures against the vertebrate host include vaccination of pigs and location of piggeries away from human dwelling. The most effective method of JE control is through vaccination (**Table 1**) of the human host. It must be realized though, that human vaccination does not interrupt the natural cycle of the virus, does not prevent transmission of the virus in nature and there is no herd immunity. An unvaccinated individual therefore remains susceptible to the infection. A JE control target of 0.5 confirmed JE cases per 100,000 children under 15 years of age in affected countries by 2015 has been set by PATH (2009).

Mouse Brain Killed Vaccine

This is the earliest vaccine to be manufactured against JE, originally produced by BIKEN, Japan and marketed in the US as JE-VAX. It was also produced in India at Kasauli. Since the vaccine was derived from neural tissue, a risk of neurological events did exist. Booster doses were required. A new pattern of adverse reactions in the form of urticaria, angioedema, respiratory distress and collapse due to hypotension were reported since 1989, mostly among travelers. All this led to suspension of vaccine production and all remaining doses expired in 2011.

P3 Strain Vaccine

This is a formalin inactivated, cell culture-derived, JE vaccine based on the Beijing P-3 strain. The vaccine was in wide use in

Table 1 Vaccines for Japanese encephalitis

Vaccine	Schedule	Dose	Remark
Mouse brain killed vaccine	2 doses up to 4 weeks apart	0.5 mL for children aged 1–2 years; 1.0 mL for children aged 3 years and older	Expensive, short supply, adverse effects, production stopped
P3 inactivated vaccine	2 doses and booster every 3 years	0.5 mL for 6–12 months of age, then boosters at 1 year, school entry, and at the age of 10 years	Low immunity, need for boosters
Live attenuated vaccine	Single dose/2 doses 1 year apart	0.25 mL for 2 months through 3 years, 0.5 mL for 3 years of age and older	Good immunity even after 5 years; WHO prequalified in 2013
Ixiaro	2 doses 28 days apart and booster after 1 year	0.25 mL for 2 months–2 years, 0.5 mL for 3–16 years of age and 0.5 mL for ≥ 17 years of age	Full duration of protection after primary immunization is unknown
Vero cell-derived purified inactivated JE vaccine from Indian strain of the virus (821564 XZ)	2 doses up to 4 weeks apart starting from 1 year of age.	0.5 mL each	Since appreciable waning was noted in both seroconversion and seroprotection rates, there is definitely a need of booster dose at later stage
Chimeric vaccine			Premembrane and envelop (prME) genes of an attenuated human vaccine strain (SA-14-14-2) of JE virus inserted between core and nonstructural genes of a Yellow Fever 17D infectious clone. Phase III trials underway

China since the 1960s. The relatively low efficacy and need for repeated booster doses led to the vaccine being replaced by the live attenuated vaccine.

Live Attenuated Sa-14-14-2 Strain Vaccine

This is the only live attenuated JE vaccine currently available. It is being used in the public sector in China since 1998, Nepal (since 1999) and India (since 2006). Studies conducted in Nepal reported efficacy of 99.3% in the same year, 98.5% after 1 year and 96.2% after 5 years. An Indian study found vaccine efficacy to be 94.5% after 6 months. Adverse effects are seen in only 5–10% recipients—transient fever, local reactions, rash or irritability. This vaccine was imported by the Government of India from China after the Uttar Pradesh epidemic of 2005. It was used in campaign style vaccination drives for children 1–15 years of age in Uttar Pradesh and later incorporated in the national immunization program. Dose is 0.5 mL given subcutaneous. The initial vaccine strain did not meet WHO prequalification standards but recently this vaccine manufactured in China in partnership with global health organization PATH has met WHO prequalification standards.

IC51 Vaccine–Ixiaro

This is a new generation formalin inactivated vaccine manufactured by Intercell (Austria) and distributed by Novartis Vaccines. It is prepared from the SA-14-14-2 strain grown in Vero cells. This is the only JE vaccine to have received US Food and Drug Administration (FDA) approval for use in adults 17 years of age or older in 2009 and children beyond 2 months age since 2013. This vaccine was licensed in the US on the basis of its ability to induce JE virus neutralizing antibodies as well as safety evaluations in almost 5,000 adults. Protective neutralizing antibodies developed in 96% of adults after schedule of 2 doses 28 days apart. Local symptoms of pain and tenderness were the most commonly reported symptoms in a safety study with 1,993 adult participants. Post licensure studies and surveillance are ongoing to further evaluate the safety of Ixiaro in a larger population. This vaccine is available in India as JEEV (Biological E Ltd). Schedule is 2 doses 28 days apart followed by a booster after 1 year. Dose is 0.25 mL below 3 years and 0.5 mL beyond.

Indian Strain Vaccine

Another Vero cell-derived purified inactivated JE vaccine is developed from an Indian strain of the virus (821564 XZ) isolated in Kolar, Karnataka, during the early 1980s and characterized by the National Institute of Virology, Pune. This vaccine was developed through public-private partnership between the Indian Council of Medical Research and Bharat Biotech Ltd. It has received manufacturing and marketing approval from the Drug Controller General of India. It is being marketed by the name JENVAC.

Chimeric Vaccine

Live attenuated chimeric JE vaccine using SA14-14-2 strain and yellow fever 17 D virus has been developed and undergone trial in India. The premembrane and envelop (prME) genes of an attenuated human vaccine strain (SA-14-14-2) of JE virus are inserted between core and nonstructural genes of a YF 17D infectious clone, resulting in a live chimeric vaccine.

MORE ON THIS TOPIC

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IN A NUTSHELL

1. Japanese encephalitis, the single largest cause of viral encephalitis in the world today, is primarily an Asian disease.
2. It occurs in annual outbreaks in most of southern and eastern India.
3. Japanese encephalitis is a zoonosis with its natural cycle in the mosquito vector and vertebrate hosts. Man is an incidental dead end host. The main vector is the *Culex tritaeniorhynchus*—a rice field breeding mosquito and the main vertebrate hosts are pig and ardeid birds.
4. The JEV is a single stranded positive sense neurotropic RNA virus with 3 structural proteins—premembrane (PrM), core (C) and envelop (E), and 7 nonstructural proteins. The E protein is related to neurovirulence. There are 5 genotypes and genotype III is most prevalent in India.
5. The clinical course of JE can be divided into 3 stages—(1) prodromal stage with nonspecific fever, headache, vomiting, diarrhea etc, lasting from a few hours to days; (2) acute encephalitic stage with continuing fever, convulsions, coma and signs of raised intracranial tension lasting 7–10 days and; (3) convalescent stage with gradual improvement over weeks to months. About 70% of survivors suffer sequelae.
6. Diagnosis is mainly by detection of JE IgM in cerebrospinal fluid or serum. Radiological features are hypodensities in thalami, basal ganglia and brain stem.
7. Differential diagnosis includes other viral encephalitides, nonviral meningoencephalitides, immune mediated encephalitis, infectious encephalopathies and functional and structural causes of coma.
8. Treatment is largely supportive.
9. WHO has coined the term *acute encephalitis syndrome* for surveillance purposes and has set surveillance standards for JE.
10. The mainstay of prevention is through vaccination. Both live and killed vaccines derived from the SA-14-14-2 strain are available. The killed vaccine grown in Vero cells has received FDA approval for use in travelers. An Indian strain killed vaccine is also available.

Chapter 31.12

Infectious Mononucleosis

Rashmi Ranjan Das

Infectious mononucleosis (IM) refers to a spectrum of clinical manifestations caused by Epstein-Barr virus (EBV), and is variably named as *Glandular fever* or *Kissing disease*. The illness commonly affects the children and adolescents. The characteristic features are prolonged fever, pharyngitis, lymphadenopathy, fatigue, myalgia and atypical lymphocytosis. Infectious mononucleosis is named because of the mononuclear lymphocytosis with atypical lymphocytes that accompany the clinical syndrome.

EPIDEMIOLOGY

The epidemiologic factors that influence the incidence and distribution of infection by EBV differ from those that cause clinical IM. The two main factors influencing infection are: levels of hygiene and cultural patterns, leading to exposure to saliva. In developing countries, pre-chewing of food for infants, and in developed countries, oral kissing in adolescent period are important modes of transmission of infection. Besides oral route, parenteral routes (blood transfusion and bone marrow transplantation) also play a role in transmission of infection. Epstein-Barr virus does not spread through environmental sources, droplets, fomites or sexual contact. The factors influencing development of IM are: age at the time of exposure, immune status, genetic factors, and psychosocial variables. Epstein-Barr virus infection without clinical IM occurs early in life in developing countries, but clinical IM is common in developed countries because of delayed exposure and infection until older childhood or young adult life.

In developing countries, most children under 5 years of age are infected with the immunity reaching almost 100% by the age of 10 years. In a study from India, IM was found to be more common during the preschool age. After acute infection, the virus is shed continuously in oral secretions for more than 6 months, followed by intermittently for life. The rate of viral shedding varies from 20–30% in healthy patients to as high as 60–90% in immunosuppressed patients. Infectious mononucleosis does not show seasonal variation.

ETIOLOGY

Infectious mononucleosis is caused by EBV, a DNA virus of the herpes family. Epstein-Barr virus causes both heterophile-positive and most of the cases of heterophile-negative IM. An infectious mononucleosis like syndrome (IMLS) may be caused by both infectious (infection due to *Cytomegalovirus*, HIV, human herpes virus 6, adenovirus, rubella, toxoplasma, *Streptococcus*, brucellosis, spirochetes, and *Salmonella*), and noninfectious conditions (drugs, autoimmune, and neoplastic diseases).

PATHOGENESIS

The EBV enters the oropharynx through salivary fluid transfer, either by kissing in adolescents or saliva-contaminated objects in children. The virus multiplication occurs locally in the epithelial cells of parotid duct, oropharynx, tongue and salivary gland tissue. This leads to an exudative pharyngotonsillitis along with sore throat. Viral multiplication in the local lymphatics often results in cervical lymphadenopathy. The virus then enters the bloodstream from one of these sources, involves B cells (through CD21 receptors), and spreads hematologically to different organs producing pertinent

clinical manifestations. Atypical lymphocytosis occurs in response to infected B cells. These are CD8⁺ T cells that exhibit both cytotoxic suppressor functions and are characteristic features of IM. This results in an inverted CD4⁺/CD8⁺ T cell ratio. The memory B cells act as reservoir of the virus in the body.

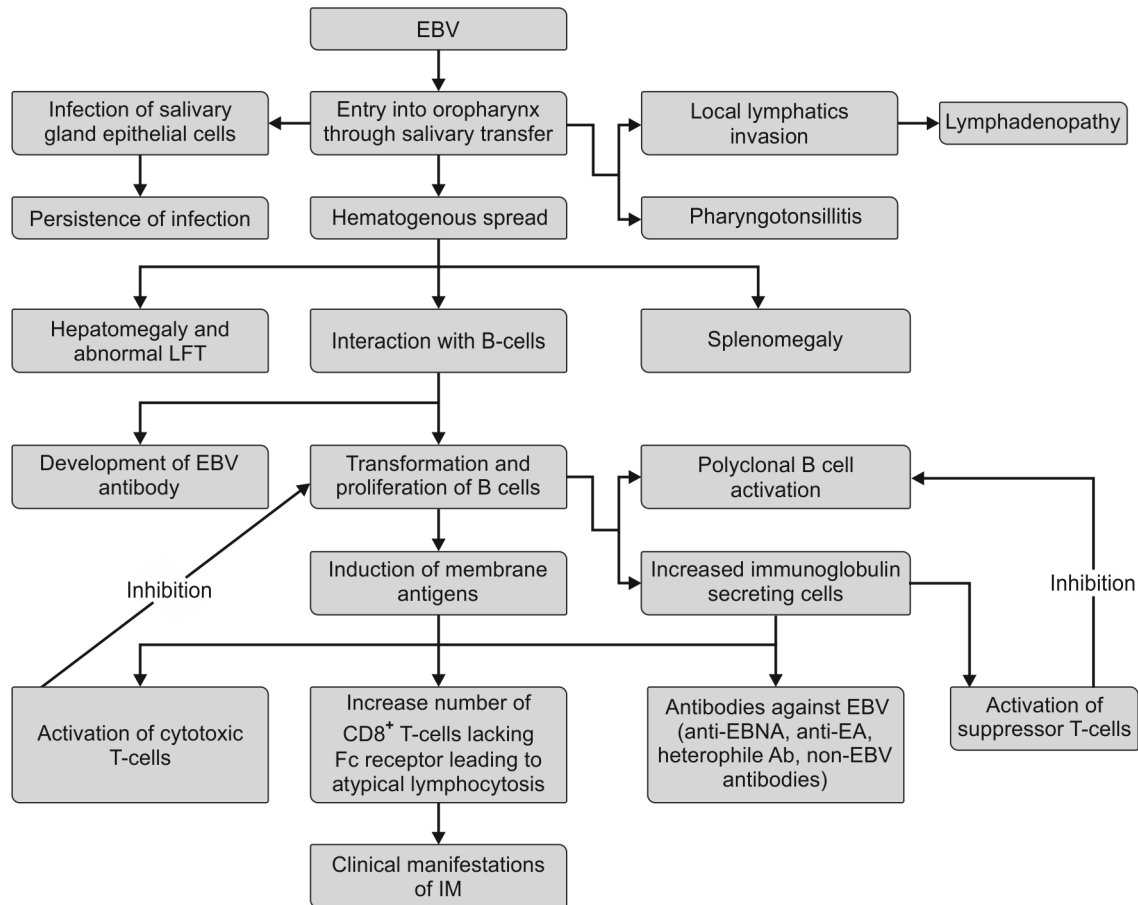
The postulated mechanisms behind development of the clinical features of IM are: B and T cell interactions, immune complex deposition or other immunopathologic events, direct effect of the virus on cells or from combination of some of these mechanisms. The rare occurrence of IM during early childhood may be because of the failure to evoke induction of neoantigens on the B-cell surface, by the virus. In older children and young adults, the T cells that respond to such neoantigens are composed largely of proliferating CD8⁺ T cells that lack the Fc receptor for IgG and IgM. Some of these T cells are cytotoxic and lyses infected cells, limiting their proliferation and accounting for the low percentage of virus-positive B cells during the acute phase of IM. The acute illness and the proliferation of B cells are limited in part by both nonspecific and antigen-specific cytotoxic T cells, along with the lymphokines they produce, and the humoral antibody.

A single attack of IM confers a high degree of durable immunity, and the second infection either occurs very rarely or not at all. As the subclinical or inapparent EBV infections confer lasting immunity, the classic disease occurs rarely. However, if the T cell immunity is compromised, endogenous reactivation occurs and the virus infected B cells may start proliferating leading to the development of clinical syndrome. The pathogenesis has been described schematically in **Flow chart 1**.

CLINICAL FEATURES

The exact incubation period of IM in children is not known, but may be shorter than the 4–8 weeks period seen in adolescents. Nonspecific features like malaise, fatigue, and myalgia for 1–2 weeks may precede the onset of fever, sore throat/pharyngitis, and lymphadenopathy. Low-to-moderate degree of fever commonly occurs in the first 2 weeks of the illness, sometimes persisting for more than 1 month. Sometimes, the fever may be associated with chills and rigors, thus mistaken as malaria in the initial period. Infectious mononucleosis is also one of the common causes of pyrexia of unknown origin (PUO). The pharyngitis is often associated with whitish or gray-green exudates having an offensive odor. The eyelids may be swollen, and petechiae occur on the hard palate in 5–7% cases.

The median frequency of symptoms is as follows: sore throat (75%), malaise (47%), headache (38%), abdominal pain, nausea or vomiting (17%) and chills (10%). The median frequency of signs is as follows: lymphadenopathy (95%), fever (93%), pharyngotonsillitis (82%), splenomegaly (51%), periorbital edema (13%), hepatomegaly (11%), rash (5%) and jaundice (5%). Deranged liver function tests occur as a common finding but symptomatic hepatitis or jaundice is rare. In the first and second week of illness, pharyngotonsillitis and lymphadenopathy are most prominent. In the second and third week of illness, splenomegaly is more prominent. Though posterior cervical lymph nodes are most commonly affected, generalized lymphadenopathy sometimes occur in IM. The lymph nodes are enlarged, symmetrical, may or may not be tender and are neither matted nor fixed. Epitrochlear lymphadenopathy has also been described with relatively increased frequency. In approximately 5% cases, a morbilliform or papular erythematous rash develops on upper extremities or trunk. One of the characteristic features is the development of *ampicillin rash* after administration of ampicillin or amoxicillin in 80% cases. This rash is vasculitic in nature developing secondary to immune complex deposition, and resolves spontaneously without treatment.

Flow chart 1 Proposed pathogenesis of EBV leading to infectious mononucleosis

Abbreviations: LFT, liver function test; Ab, antibody; EBNA, Epstein-Barr nuclear antigen; EA, Epstein-Barr early antigen; EBV, Epstein-Barr virus; IM, infectious mononucleosis.

COMPLICATIONS

Few patients with IM experience complications in the initial 2 weeks of illness. Complications that can lead to death are those related to: upper airway obstruction, central nervous system, splenic rupture and septic shock (bacterial superinfection). In one study, children having fever for more than 14 days were at an increased risk of complications, and septic shock was common in those having high VCA-IgM antibody titer. The rate of splenic rupture in children is probably much lower than the adult rate of less than 0.5%. The rupture is either spontaneous or preceded by trivial trauma. There may be marked swelling of the oropharyngeal lymphoid tissue and tonsils causing airway obstruction manifest as breathing difficulty and/or stridor. Though uncommon (incidence is <5%), it is one of the most common indications for hospitalization.

DIFFERENTIAL DIAGNOSES

Though EBV causes most of the heterophile positive and negative cases of IM, infectious mononucleosis like syndrome (IMLS) is caused by cytomegalovirus (CMV), toxoplasma, adenovirus, viral hepatitis, HIV or other agents. Cytomegalovirus causes most of the heterophile negative mononucleosis syndromes. Compare to classic IM, IMLS is associated with a lower frequency of lymphadenopathy, pharyngotonsillitis and splenomegaly. Streptococcal pharyngitis is the most common differential diagnosis, and any failure of improvement within 48–72 hours

of treatment should raise suspicion of IM. The differential diagnoses are summarized in **Table 1**. When complications like extremely high or low total leukocyte counts, moderate-to-severe thrombocytopenia, and hemolytic anemia occurs, a thorough investigation including bone marrow examination is justified to exclude any serious underlying cause. Other rare differential diagnoses include infections (due to human herpes virus 6, rubella, *Brucella*, spirochetes, and *Salmonella*), drugs, autoimmune diseases and neoplastic conditions (lymphoma or leukemia).

DIAGNOSIS

The accuracy (sensitivity and specificity) of clinical parameters used for the diagnosis of IM is summarized in **Table 2**. The two most important parameters that are useful in considering the possibility of IM are splenomegaly and lymphadenopathy (involving posterior cervical, axillary and inguinal lymph nodes), and in ruling out the possibility of IM are: absence of cervical lymphadenopathy and fatigue. *Hoagland's diagnostic criteria* have been widely used. Though highly specific, these criteria are not highly sensitive making them useful only for research purposes. The criteria include following parameters: lymphocytosis (50% of differential counts with 10% being atypical lymphocytes) *plus* fever, lymphadenopathy and pharyngitis *plus* a positive serological test.

Routine Laboratory Tests

Hemoglobin is normal (anemia is rare in IM). The total leukocyte count is commonly increased to the range of 10,000–20,000/mm³, of which more than 60% are lymphocytes (atypical lymphocytes

Table 1 Differential diagnosis of infectious mononucleosis like syndrome (IMLS) with key features

Causes of IMLS	Differentiating features
Viral pharyngitis (influenza, adenovirus)	Fever, lymphadenopathy, and tonsillar exudate are less common, but cough and rhinorrhea are more common. Splenomegaly and palatal petechiae are unlikely. ESR normal.
Streptococcal pharyngitis	Lymphadenopathy is usually anterior cervical and submandibular, compared to posterior cervical in IM. Fatigue and malaise is less prominent. Splenomegaly and palatal petechiae are unlikely. ESR normal. Responds to antibiotics in 48–72 hours.
Cytomegalovirus infection	Fever, lymphadenopathy, tonsillar exudate are less common. During acute illness, significant elevation in IgM or a fourfold increase in antibody IgG titers in paired sera.
Toxoplasmosis	Fever, lymphadenopathy, tonsillar exudate are less common. During acute illness, significant elevation in IgM or a fourfold increase in antibody IgG titers in paired sera.
Acute human immunodeficiency virus infection	Opportunistic infections, skin rash, weight loss, nausea, vomiting, diarrhea, low CD4 ⁺ T cell count

Table 2 Accuracy of clinical parameters in the diagnosis of infectious mononucleosis

Clinical parameters	Sensitivity (%)	Specificity (%)
Splenomegaly	7	99
Any cervical lymphadenopathy	87	58
Anterior cervical lymphadenopathy	70	43
Posterior cervical lymphadenopathy	40	87
Axillary lymphadenopathy	27	91
Inguinal lymphadenopathy	53	82
Fever	27	84
Fatigue	93	23
Headache	60	55
Palatal petechiae	27	95

Table 3 Serological features of infectious mononucleosis

Phases of illness	Heterophile Ab (Paul-Bunnell, Monospot)	Anti-VCA Ab		Anti-EA Ab		
		IgM	IgG	EA-Diffuse	EA-Restricted	Anti-EBNA Ab (IgG)
Acute phase	+	+	++	+	–	–
Convalescent phase	±	–	+	–	±	+
Past infection	–	–	+	–	–	+
Reactivation or chronic active phase	–	–	++	+	+	±

Abbreviations: Ab, antibody; VCA, viral capsid antigen; EA, early antigen; EA-D, antibody to EA in diffuse pattern; EA-R, antibody to EA in restricted pattern; EBNA, Epstein-Barr nuclear antigen.

being around 20–40%). Thrombocytopenia with the platelet count in the range of 50,000–150,000/mm³ occurs in more than 50% of patients but clinical bleeding (petechiae or purpura) is rare. Erythrocyte sedimentation rate might be elevated. Deranged liver function test commonly manifesting as transaminitis with normal or slightly increased bilirubin occurs in 50% of uncomplicated cases, but clinical jaundice is rare.

Heterophile antibody test Heterophile antibodies commonly occur in the sera of patient affected with IM. Two tests are commonly employed to detect them: *Paul-Bunnell test*—the sheep red blood cells (RBCs) agglutinate in the presence of heterophile IgM antibodies, and *Monospot test (latex agglutination assay)*—the horse RBCs agglutinate in the presence of heterophile IgM antibodies. Monospot test has a sensitivity of 85% and specificity of almost 100% if performed after first week of illness. These are often the first tests ordered for the diagnosis of acute IM. These tests are less useful in younger children less than 2–4 years of age. If these tests are negative but IM is strongly suspected then EBV-specific antibody testing should be done to confirm the diagnosis. Heterophile-negative IM means any patient who remains heterophile-negative for more than 6 weeks after diagnosis of IM.

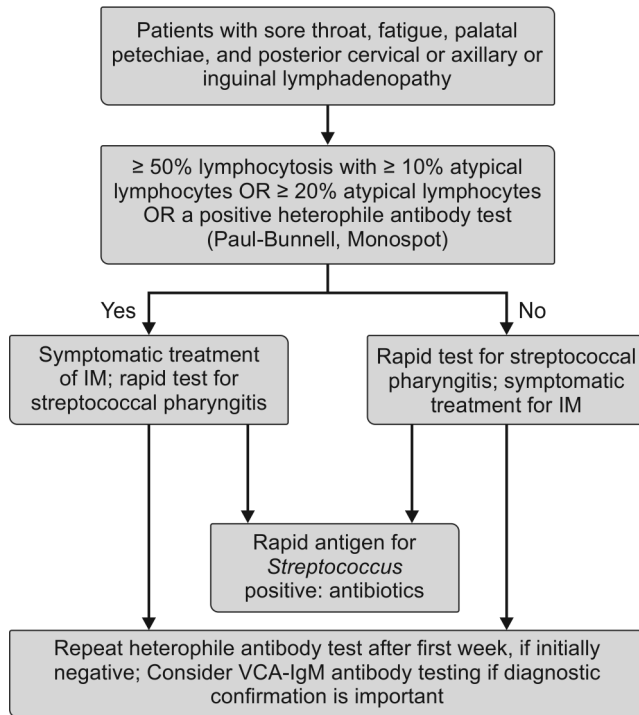
EBV-specific antibodies These tests are indicated for confirmation of either an acute infection (including heterophile negative cases) or a past infection. Viral capsid antigen (VCA), nuclear antigen (EBNA), and early antigen (EA) are the widely used tests. The VCA-IgM and IgG antibody tests are the most useful in confirming the diagnosis of acute infection and differentiating it from previous infection. The VCA-IgM antibody sometimes may be detected up to 3–6 months after acute infection. Presence of rheumatoid factor may result in a false-positive VCA-IgM test. VCA-IgG level rises later in the acute phase, then declines gradually, persisting with variable titer throughout the life. Antibody to EBNA is detectable 6–8 weeks after the onset of symptoms, and has the same significance as VCA-IgG in distinguishing acute from previous infection. Early antigen is present in early phase and is less useful for diagnosis of IM. Serological features of IM are described in **Table 3**.

Diagnostic Approach

There is no consensus or evidence-based guideline available presently for evaluation of a suspected case of IM. A simple diagnostic approach based on the present available evidence may be followed as shown in **Flow chart 2**.

MANAGEMENT

Good supportive care is the mainstay of treatment that includes control of fever and myalgia by paracetamol or non-steroidal anti-inflammatory drugs (NSAIDs), maintenance of adequate hydration, and administration of lozenges or local anesthetic spray (2% xylocaine) or gargling to relieve sore throat/pharyngitis.

Flow chart 2 Algorithm for the management of suspected infectious mononucleosis

Clinical trials suggest that strict bed rest with severe activity limitation may delay the recovery from illness. So, it seems reasonable to advise patients against strict bed rest, and to resume various activities based on the energy levels. Contact sports and strenuous physical activities should be particularly avoided during the initial 2–3 weeks of illness or till splenomegaly is present, in order to avoid splenic rupture.

A systematic review analyzing the data on acyclovir found less oropharyngeal shedding of the virus at the end of treatment. As acyclovir did not provide any significant clinical benefit, it is not recommended for the treatment of IM. One trial tested the combination of acyclovir and prednisolone, but this combination did not reduce the duration of symptoms significantly and hence not recommended in the treatment.

Because of the unpredictable course of illness, oncogenic complications associated with the virus, and the risk of bacterial superinfection, steroid therapy is not generally indicated for an uncomplicated case of IM. Prednisone (1 mg/kg/day, maximum 60 mg/day) for 1 week with subsequent tapering over next 1 week may be used for life-threatening complications like airway obstruction, thrombocytopenia with bleeding, autoimmune hemolytic anemia, and severe central nervous system (CNS) (seizure, meningitis, encephalitis) manifestations.

PROGNOSIS

The prognosis for complete recovery is excellent if no complications ensue during the acute illness. In a large study on the natural history of IM, the patients were followed till 6 months. The results were as follows: fever, sore throat, headache, cough, rash and nausea resolved after 1 month of the onset of symptoms; fatigue, joint soreness and sleepiness resolved more slowly over a period of 6 months. There was also a steady improvement in the functional status requiring almost 2 months for complete functional recovery. There are several rare complications of IM that one should be

Table 4 Potential complications of infectious mononucleosis

Respiratory problems		
Upper airway obstruction		Pneumonia/pneumonitis
Hematological problems		
Hemolytic anemia		Hemophagocytic lymphohistocytosis
Thrombocytopenia		Red cell aplasia
Pancytopenia		Severe granulocytopenia
Neurological abnormalities		
Meningitis		Encephalitis
Guillain-Barré syndrome		Reye syndrome
Cranial nerve palsies		Retrobulbar neuritis
Acute disseminated encephalomyelitis (ADEM)		Ataxia
Alice in wonderland syndrome (metamorphopsia)		Seizure
Cardiovascular		
Myocarditis		Conduction abnormalities
Others		
Hepatitis	Interstitial nephritis	Genital ulcer
Splenic rupture	Pancreatitis	Bacterial superinfection

aware of, and these are mentioned in **Table 4**. Studies have found that, a higher VCA-IgM titer ($>100 \mu\text{mL}$) and female gender are associated with an increased risk of complications.

PREVENTION

As the virus is transmitted through saliva, close contact with saliva may be avoided during the acute phase. There is no role of isolation of the patient and is not recommended. There is no vaccine available against EBV. Clinical trials are undergoing presently to find a suitable vaccine.

IN A NUTSHELL

1. Infectious mononucleosis should be suspected in any patient with sore throat, fatigue, palatal petechiae, lymphadenopathy (posterior cervical or axillary) and splenomegaly.
2. Relative lymphocytosis ($>50\%$ lymphocytes) including 10% atypical lymphocytes or at least 20% atypical lymphocytes or a positive heterophile antibody test favors the diagnosis.
3. When the diagnosis of IM is suspected, a heterophile antibody (monospot) test should be ordered first, and a negative test should be repeated after 1 week for further confirmation.
4. When diagnosis confirmation is important or in heterophile negative cases, VCA-IgM antibody testing is recommended.
5. Infectious mononucleosis like syndrome (IMLS) including toxoplasmosis, streptococcal infection, CMV or other viral infections may show negative heterophile antibody test.
6. Good supportive care is the mainstay of treatment, and includes antipyretics or analgesics, adequate hydration, gargling or lozenges and bed rest.
7. There is no role of steroid or acyclovir in the routine uncomplicated cases of IM, although steroids may be used for life-threatening complications like airway obstruction or bleeding or CNS manifestations.
8. Contact sports or strenuous physical activity should be avoided during the initial 2–4 weeks of illness to avoid splenic rupture.
9. Few symptoms like fatigue, myalgia, joint soreness and sleepiness may persist up to 6 months following resolution of the acute illness.

MORE ON THIS TOPIC

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Chapter 31.13

Enteroviral Infections

Annapurna Sudarsanam

Enteroviruses (EVs) along with rhinoviruses (RVs) are the commonest cause of viral infections in childhood. EVs are implicated in a wide range of human diseases including aseptic meningitis, acute flaccid paralysis (AFP), vesicular and exanthematous skin lesions, myocarditis, pleurodynia, severe generalized disease of the infants and undifferentiated febrile illness. Subclinical infection is by far the most common infliction.

ETIOLOGY

Enteroviruses of human origin include the following species:

- Poliovirus, types 1–3
- Coxsackie A virus, types 1–24 (no type 23)
- Coxsackie B virus, types 1–6
- Echovirus (E), types 1–33 (no type 10, 22, 23 or 28)
- Enterovirus, types 68–71.

Enteroviruses were originally classified by their antigenic and pathogenic properties in humans and mice. Since the 1960s, new EVs have been assigned numbers rather than being classified as coxsackievirus (CV) or echovirus. E-22 and E-23 have been reclassified as parechovirus. A new system of classification based on genetic relatedness divides the EV into types A–D. The virion consists of a 28–30 nm icosahedral capsid shell made of 60 subunits each comprising of four proteins VP1–4 surrounding a single-stranded positive-sense RNA. EVs are relatively resistant to common disinfectants like 70% ethanol, dilute lysol, isopropanol, quaternary ammonium compounds. They are insensitive to lipid solvents like chloroform and ether. Formaldehyde, glutaraldehyde, free residual chlorine, hypochlorite, strong acid and UV light can inactivate them. Although relatively thermostable, most EVs are inactivated at 42°C making it possible to use pasteurization to inactivate them.

EPIDEMIOLOGY

Host Factors

Rate of infection is highest in the first 12 months of life. Most of the enteroviral meningitis occurs in the first 4 months of life and majority of the severe EV71-associated brainstem encephalitis occurs in first 2 years. Male sex has been associated with a greater risk of enteroviral infection in infancy and childhood by almost a factor of two. Factors that increase susceptibility to enteroviral infections include age, male sex, low socioeconomic status, overcrowding and poor hygiene. Vertical transmission of maternal antibodies or through breastmilk is protective for the first 3–6 months. Human leukocyte antigen (HLA)-A33, which is a common phenotype in Asian populations but rare in Caucasians, has been associated with increased susceptibility to EV71 infection. HLA-A33 (class I) and HLA-DR17 (class II) may also contribute to the severity of the disease caused by human enterovirus 71 (HEV71) infection.

Environmental Factors

Enteroviruses are ubiquitous. Whilst they circulate all year round there is a marked increase in seasonal periodicity noted over the summer and fall in the temperate climates. In the warmer areas, higher excretion rates are observed and disease occurs in an endemic pattern.

Transmission

Humans are the only reservoir for the EV. Transmission occurs mainly through close contact with an infected person via fecal-oral route or respiratory droplets. Nonimmune household contacts are at high risk for infection. Secondary attack rates may be as high as 75% within families. Crowded situations like day care centers, school, nurseries, orphanages, summer camps increase risk of quick spread and outbreaks of infections. Vertical transmission from mother to the child during delivery or via breastmilk is also known. Rarely in utero transmission has been reported. Given the hardy nature of the viruses, transmission can also occur via contaminated surfaces/fomites. Transmission via contaminated food and water is possible but rarely reported. Viruses are present in the tears and conjunctival secretions and may contribute to explosive outbreaks of acute hemorrhagic conjunctivitis due to CV-A24 and EV70.

PATHOGENESIS

Following the initial infection either via the respiratory or fecal-oral route, the virion attaches itself to the cytoplasm of the mucosal cells of the oropharynx via cell surface receptors. Following attachment to the cell surface receptor, the viral RNA is released into the cytoplasm. Translation of positive-sense RNA results in the production of a polypeptide which is further cleaved down by the virus-encoded proteinases. The proteins generated enable replication of the viral RNA after which the RNA and proteins are assembled into 30 nm virion particles. The replication process results in the generation of 10^4 – 10^5 virions which are released following cytolysis within 5–10 hours after the initial infection. Mucosal replication and cell-to-cell spread is followed by spread to the local lymphoid tissues such as the tonsils, Peyer's patches and regional lymph nodes. This is followed by a *minor viremia* with spread of the virus to the distant reticuloendothelial tissue including lymph nodes, liver, spleen and bone marrow. The levels of virus are low and transient in this phase. Host immune system especially circulating antibodies directed against the VP1 capsid proteins may limit the further spread of the virus resulting in a subclinical infection. Alternatively the virus further replicates followed by a *secondary viremia* and infection of the target organs which may be the skin, central nervous system (CNS), liver, kidneys, muscles, heart or pancreas. Tissue tropism is determined by the infecting virus serotype.

PATHOLOGY

Local tissue damage results from direct viral cytolytic effects and from the inflammatory response triggered. Meningeal infection is associated with a mononuclear pleocytosis in the cerebrospinal fluid (CSF). Encephalitis involving the white and gray matter, deep gray nuclei, brainstem and cerebellum is associated with perivascular lymphocytic infiltration, parenchymal infiltration with inflammatory cells, gliosis, neuronal phagocytosis and cell necrosis. Severe EV71 encephalitis is associated with involvement of the brainstem, spinal cord gray matter, subthalamic and dentate nuclei. In severe cases, it has been associated with neurogenic pulmonary edema, interstitial pneumonitis and cardiac failure due to sympathetic overactivity. Myocarditis with enteroviral infection is characterized by mixed inflammatory infiltrate. Macrophages predominate in the early stages and contribute to viral clearance. Natural killer cells and T lymphocytes cause necrosis of the infected myocytes. Persistence of viral infection of the myocardium has been linked to dilated cardiomyopathy. Immunocompromised patients, especially those with humoral immunodeficiency, are vulnerable to severe disease and also suffer from chronic EV infections. A role of molecular mimicry and bystander damage,

i.e., upregulation of the nonspecific immune response by the virus has been suggested in explaining some of the pathogenic effects of enteroviral infections including CV-B4 associated diabetes mellitus (DM) and CV associated myocarditis.

Immunity

Enteroviral infection is followed by the development of serotype specific immunoglobulin M (IgM) antibodies. More long-term immunity is provided by IgG and IgA which also provides mucosal immunity. Reinfection with the same serotype may occur but it does not proceed to clinical infection and the duration of viral shedding is also much shorter. However, there is evidence to suggest infection by a different serotype may be enhanced by the presence of heterotypic antibodies.

CLINICAL FEATURES

The incubation period for EV is 3–6 days except for acute hemorrhagic conjunctivitis for which the incubation period is 1–3 days. Viral shedding via the respiratory route from infected children persists for 1–3 weeks while that from the fecal route may persist for 7–11 weeks. Majority of the enteroviral infections are asymptomatic and the most common clinical feature would be an undifferentiated febrile illness. However, the EVs have been associated with a myriad of acute and chronic illnesses. A variety of EV can cause the same disease manifestation or there may be a typical illness pattern associated with a particular serotype. Outbreaks of illnesses may be associated with several circulating serotypes at the same time.

Nonspecific Febrile Illness

This is the most common manifestation of enteroviral illness. The typical symptoms include abrupt onset fever 38.5–40°C (101–104°F) associated with irritability, lethargy, poor feeding, vomiting, diarrhea, rhinorrhea, with or without a rash. EV infection can cause respiratory distress, pneumonia, otitis media, bronchiolitis, croup, parotitis, and pharyngotonsillitis which may be exudative. Genitourinary manifestations such as orchitis and epididymitis are possible. A variety of exanthems may be associated with EV including macular, maculopapular, vesicular, urticarial rashes and papular acrodermatitis. Older children may present with headache and myalgia. Almost all the infants recover in 7 days without sequelae. New infection with a different EV serotype is not uncommon. Enteroviral exanthems typically occur in children less than 10 years. The younger the age the more common it is. Petechial and purpuric rashes have been associated with E-9 and CV-A9 that can be confused with meningococcal disease.

Hand, Foot and Mouth Disease

The hand, foot and mouth disease (HFMD) is a highly contagious viral illness and is one of the classic exanthematous diseases associated with EV that affects predominantly children. Fever and sore throat may be the initial symptoms followed by the appearance of a typical rash that is maculopapular or vesicular on the hands and feet (**Fig. 1**) and oral ulcerations. Oral lesions involve the tongue, buccal mucosa, gingiva, posterior pharynx, palate and lips. Maculopapular-vesicular rash may also be present on the buttocks and groin. The typical illness is short lasting associated with no to mild fever. The vesicles start drying in a week's time. Majority of the HFMD cases are associated with CV-A16 and EV71. Since the year 2000, several large HFMD outbreaks have been reported in many Asian regions such as China, Malaysia and Vietnam. Smaller outbreaks have been reported from parts of India since 2004. The EV71 HFMD tends to be more severe and may be associated with a severe progressive form associated with neurological and cardiopulmonary complications. Other EV serotypes, CV-A4–7,



Figure 1 Hand, foot and mouth disease
Source: Dr Madhumita Banik, Kolkata, India.

CV-A9–10, CV-B1–3, CV-B5, E-4 and E-19, have also been found associated with both sporadic infections and outbreaks of HFMD. CV-A6 in recent outbreaks has been associated with classical HFMD as well as with an atypical perioral or more generalized distribution of rash or a vesiculobullous rash type. Children with eczema may be more affected and *eczema coxsackium* was coined as far back as 1968 for this condition. Postinfectious loss of the nails is reported frequently.

Herpangina

Herpangina is an enanthem associated with EV typically coxsackie A virus and occasionally some coxsackie B serotypes and echoviruses. The illness is characterized by abrupt onset high-grade fever with sore throat, odynophagia, vomiting and headache. The typical lesions present as grayish bumps 1–2 mm in size mainly over the tonsillar pillars, tonsil, posterior pharynx, uvula and soft palate. They ulcerate within a day or two forming shallow ulcers up to 5 mm in size with an erythematous border. The illness is usually self-limiting and clears in about a week. Occasional cases of association with aseptic meningitis have been reported.

Acute Hemorrhagic Conjunctivitis

This was first reported in 1969 from Ghana. Several outbreaks have since been reported from Japan, Singapore, India, the United States of America, China, Cuba, Pakistan, Egypt and Thailand. Epidemiologic studies have implicated CV-A24 and EV70 strains as causative agents. A large epidemic involving over 200,000 people was reported from Brazil in 2006. The illness is characterized by conjunctival congestion, eye pain, blurred vision, excessive tearing, vascular dilatation and chemosis, followed by appearance of subconjunctival hemorrhage. The illness runs a 5- to 7-day course and usually resolves without any sequelae. Superadded bacterial infection may occur. Rarely neurologic complications like aseptic meningitis and AFP have been reported. Older children between 10 years and 14 years tend to be at the highest risk. The disease is highly contagious. Apart from fecal-oral transmissions, direct ocular transmission through contaminated tears can occur.

Other ocular manifestations of enteroviral infections in children include uveitis, optic neuritis, chorioretinitis and unilateral maculopathy. EV uveitis is a new infant eye disease that was first observed in 1980. Three distinct subtypes of human echoviruses, E-19/K, E-11/A and E-11/B, caused five hospital outbreaks in different Siberian cities in 1980–1989, affecting approximately 750 children, predominantly below 1 year of age.

Meningitis and Encephalitis

Enteroviruses are the most common cause of viral CNS infections. All enteroviral genera and almost all serotypes show neurotropism. Aseptic meningitis is the most common CNS infection. Echoviruses and group B CVs account for over 90% of the cases of viral meningitis. Risk of infection seems to be highest in the first year of life. Older children may develop a biphasic illness with an initial prodrome of fever and sore throat followed by abrupt onset of fever and headache. Encephalitis is characterized by alteration of consciousness, neurological weakness and focal seizures. Hemichorea and acute cerebellar ataxia have been reported in infants and toddlers with coxsackie A viral encephalitis. Complications such as febrile seizures, focal seizures, lethargy, coma and movement disorders can occur in 5–10% cases. Viral meningitis can be inferred from CSF analysis. The CSF white cell count can vary from 10 to over 1,000 with early polymorph predominance in the first 2 days of the illness followed by a lymphocytic predominance. Viral cause can be confirmed through viral isolation in cell culture or by polymerase chain reaction (PCR). Subtle impairment of motor function such as motor incoordination, muscle spasm or restriction of passive motion may persist for few weeks after the acute illness but generally the long-term neurocognitive outcome is good. Prominent neurologic complications with EV71 include not only aseptic meningitis with or without encephalitis, but also, more rarely, acute flaccid poliomyelitis-like paralytic disease, opsoclonus-myoclonus syndrome, benign intracranial hypertension and brainstem encephalitis. In 2012, EV71 caused particularly severe disease with brainstem encephalitis-associated cardiopulmonary dysfunction and death in young children in Cambodia. Neuroimaging and electroencephalographic (EEG) changes reflect the extent and severity of the involvement. Although majority make full recovery neurologic sequelae and rare deaths can occur. Factors associated with severe, especially fatal disease, were young age, male gender, high white count, prolonged high fever, high glucose, high C-reactive protein (CRP) and neurological findings.

Acute Flaccid Paralysis

Although poliovirus is the typical EV associated with AFP, several nonpolio EVs have in more recent times been associated with AFP. EV71 has been associated with outbreaks and is the chief viral cause of AFP in postpolio eradication era. The anterior horn cell destruction tends to be less severe than with poliovirus with a better recovery rate. EV70 has also been associated with AFP. It can specifically be associated with cases of bulbar palsy. A recent study from Kerala and Karnataka based on data collected from the Polio Surveillance Program suggested a high nonpolio EV positivity rate amongst AFP cases with a high genotype diversity among the isolates. Nonpolio EV positive AFP cases were significantly higher in children aged less than 2 years; with residual paralysis; in summer months; and in regions with relatively hot climate. A newly defined serotype EV94 was isolated from cases of AFP in Congo. EV-B106 and EV-B93 have also been isolated from AFP cases in China, Pakistan and Bolivia.

Pleurodynia or Bornholm Disease and Myositis

Pleurodynia or Bornholm disease is an acute febrile illness characterized by myositis of the intercostal and abdominal muscles presenting as severe sharp, localized spasmodic chest and abdominal pain. Coxsackie B viruses, especially CV-B3 and CV-B5, have been most commonly implicated. The severity of pain can often alarm patients into seeking urgent medical advice. Severe chest pain worsened with respiratory effort may result in splinting of chest and tachypnea. Cough is not prominent. The initial presentation may include flu-like symptoms, sore throat and headache. The lung fields are clear on auscultation. Localized

muscle tenderness and swelling and a pleuritic rub may be the only clinical findings. The presentation may mimic pneumonia or pre-eruptive phase of herpes zoster. Whilst it typically runs a benign course which resolves in 4–6 days rare cases with optic neuritis, cardiomyopathy, myopericarditis and meningitis have been reported. It tends to affect the older children and adolescent most commonly. Periodic outbreaks with high rates of transmission occur. Analgesics and rest are the standard treatment strategies. Local infiltration of intercostal nerves with xylocaine has also been reported to be effective.

Enteroviruses have been implicated in acute and chronic myositis. The acute illness may present with acute onset fever, myalgia, and elevated muscle enzymes with or without myoglobinuria. Chronic involvement may present as a subacute or chronic progressive weakness and may present with characteristic skin involvement as dermatomyositis.

Cardiac Involvement

Enteroviruses are the most common virus group associated with myocarditis. The group B CV especially the CV-B3 is the most commonly isolated virus. Clinical presentation may be after an initial febrile flu-like illness followed by cardiac symptoms in the form of chest pain, dyspnea and malaise. A pericardial friction rub may be audible. A gallop rhythm may be present with heart failure. The electrocardiogram (ECG) may show nonspecific ST segment and T wave changes. Various types of arrhythmias and conduction blocks may occur. Creatinine kinase and cardiac troponin may be elevated. Chest X-ray may show an increased cardiothoracic ratio and evidence of heart failure. Magnetic resonance imaging (MRI) and echocardiogram may be useful in assessing the severity and extent of cardiac involvement. The prognosis is better in children than adults with a case fatality rate of ~15%. Up to 10% may go on to develop persistent infection or residual myocyte damage leading to a dilated cardiomyopathy. The persistent viral infection may trigger an immune response that can foster the disease. Symptomatic and supportive management with rest, analgesia, management of arrhythmias and heart failure is the main stay of management. Pleconaril, the experimental antiviral drug has been used in small number of patients with some benefit. Use of intravenous immunoglobulin (IVIG) and other immunosuppressive therapy has not shown to produce a consistent benefit. Milrinone has been useful in severe EV71-associated cardiopulmonary failure. For those with dilated cardiomyopathy and chronic congestive heart failure, cardiac transplantation may be needed.

Neonatal Infection

Enterovirus infections are common in the neonatal period, and most cases are either asymptomatic or minimally symptomatic and without long-term sequelae. In a minority of cases, characterized by hepatic or cardiac involvement, EV infection may be severe or fatal. Immaturity of the innate immune system which may fail to limit the initial enteroviral replication makes neonates vulnerable. The severity of the infection is also dependent on the presence or absence of passively transferred maternal type specific immunity. The dominant mode of transmission of serious neonatal infection is likely at the time of delivery through contact with maternal blood, fecal material, or vaginal or cervical secretions. Transplacental infection can occur in utero. Nosocomial infections also occur in nurseries if adequate precautions are not taken. Initial presentation may be as a febrile, irritable or lethargic neonate with poor feeding. Those with severe disease may progress to develop myocarditis, encephalitis or fulminant hepatitis. Prematurity, maternal illness, early age of onset of illness (younger than 7 days of age), higher WBC count ($15 \times 10^9/L$ or greater) and low hemoglobin (10.7 g/dL or lower) have been associated with severe disease.

Neonatal myocarditis is most commonly caused by coxsackie B serotype 1–5 and less commonly by E-11. After the initial prodrome, neonates rapidly progress to overt heart failure. Seizures, bulging fontanel and CSF pleocytosis may occur with encephalitis. Cyanosis and hypotension are poor prognostic signs. Mortality rates may be 30–50%.

Fulminant neonatal hepatitis may occur with E-11 infection and can present as an enteroviral sepsis syndrome with progressive jaundice, hypotension and bleeding leading to multiple organ failure. The illness carries a high mortality despite maximal intensive care. Extensive hemorrhage into the cerebral ventricles, pericardium and interstitium of various solid organs may be found. Apart from supportive therapy, blood products, IVIG and pleconaril have been used on an anecdotal basis with some benefit.

Diabetes Mellitus

The role of enteroviral infections in type 1 DM has been investigated in epidemiological and animal studies. There is evidence to suggest an increased risk for beta-cell autoimmunity and hence type 1 DM after EV infection especially CV-B1 infection. The recent discovery of *IFIH1* gene, which is an innate immune system receptor for EV as a risk gene for type 1 DM further lends evidence to this potential link. Infection with CV-B6 and CV-B3 has been associated with a reduced risk. The association is interesting and offers potential for prevention of diabetes through development of vaccines against specific enteroviral types.

DIAGNOSIS

Most enteroviral infections go undiagnosed or a fairly certain presumptive diagnosis is established based on the characteristic clinical presentation in the context of a seasonal outbreak. Specific diagnostic tests may be useful in epidemiological studies, infection surveillance or in a very sick or unwell child to direct appropriate treatment or in postmortem samples from cases of myocarditis, neonatal infections and encephalitis. Three main diagnostic methods are the *viral cell cultures* which is the gold standard but time consuming and less sensitive, nucleic acid assays based on *reverse transcriptase PCR (RT-PCR)* or *serology*.

Viral shedding in stools may persist for 7–11 weeks and contribute to a false-positive test.

A cloned EV complementary DNA prepared from the highly conserved 5' region of the EV genome can be used for rapid and sensitive group-specific diagnosis of EV infections. The RT-PCR can detect the virus fairly quickly within 2–4 hours from small amounts of biological specimens. Serological diagnosis relies on demonstration of a fourfold rise in the titers of specific neutralizing antibodies between acute and convalescent phases. Serological assays using microneutralization techniques or complement fixation, enzyme immunoassays or indirect fluorescent antibody assays are available. Serological tests are less useful than RT-PCR or viral cultures.

VIRUS PERSISTENCE

Persistent EV infection has been demonstrated in immunodeficient and less commonly in the immunocompetent host. Patients with immunodeficiency, especially X-linked agammaglobulinemia or hypogammaglobulinemia, can develop a chronic nonpolio EV-induced aseptic meningitis or meningoencephalitis. These patients may have an associated dermatomyositis type syndrome with inflammation of multiple organs. Persistence of EV or the EV genome has been reported in immunocompetent humans and animals with varied diseases including chronic dilated cardiomyopathy, inflammatory muscle disease (myositis) and diabetes. In addition, EVs including poliovirus have been implicated in the cause of postpolio syndrome and amyotrophic lateral sclerosis.

TREATMENT

In the absence of availability of specific licensed antienteroviral drug therapy, the management of most of the enteroviral illness is symptomatic and supportive. In addition, a great majority of the infections are self-limited and do not require specific therapy. Exceptions to this situation are severe illnesses including neonatal infections, encephalitis, acute myocarditis and infections in the immunocompromised. Use of IVIG has been trialled on the presumptive basis of presence of specific neutralizing antibodies and also for nonspecific anti-inflammatory effects. Retrospective reviews suggest benefit when given early in severe diseases such as EV71-associated encephalitis. Studies have shown substantial reduction in concentrations of some proinflammatory cytokines after IVIG in EV71 encephalitis with autonomic dysfunction but not in less severe cases. IVIG has therefore become more routinely used in the treatment of severe EV71 disease and has been incorporated into the national guidelines in Taiwan. Pooled immunoglobulin delivered intravenously or via a shunt into the spinal fluid has also been used in patients who are agammaglobulinemic with chronic encephalitis and meningitis associated with nonpolio EV. Use of corticosteroids and immunosuppressive drugs like cyclosporine has been reported in the literature with uncertain effect.

Antiviral Therapy

Potential antiviral agents target various steps in the viral life cycle including attachment, entry, uncoating, translation, polyprotein processing, virus-induced formation of membranous RNA replication complexes and RNA-dependent RNA polymerase are currently under evaluation. Three candidate compounds are currently in development: (1) pleconaril (active against many EV), (2) V-073 (antipoliavirus) and (3) BTA-798 (active against many RVs and EV). Pleconaril remains the most promising drug which inhibits replication of most EV serotypes. It is a novel agent which integrates with the picornavirus capsid and prevents the virus from attaching to the cellular receptors and uncoating to release the viral RNA. Trials in patients with enteroviral meningitis have shown reduction in duration and severity of headaches and other symptoms with shorter period of viral shedding. Trials in B-cell deficient people with persistent enteroviral infections and in those with potentially fatal illness including neonates, and those with acute myocarditis have suggested substantial benefits. Mutant viruses resistant to the drug can arise. Ribavirin and lactoferrin have also shown potential benefits in *in vitro* and *in vivo* studies. Herbal products like geraniin have also shown similar potential.

PREVENTION

Good simple hygiene measures are of primary importance in preventing spread of EVs especially during outbreaks. These measures involve regular hand washing with soap and water, careful disposal of nappies of infected children, disinfecting contaminated surfaces, keeping affected children away from day care centers, schools and nurseries. Pregnant women should avoid contact with people suspected to have enteroviral illness. Isolation is warranted in hospital and neonatal unit settings.

Prophylactic administration of immunoglobulins may be beneficial to neonates in case of maternal infection. Maintenance antibody replacement with high-dose IVIG for patients with hypogammaglobulinemia has reduced the incidence of chronic EV meningoencephalitis.

A Vero cell-based inactivated human EV71 vaccine has been developed with the use of EV71 strain H07 (subgenotype C4) as the seed virus. The vaccine has completed phase III trial successfully providing effective protection against EV71-associated (but not

to other serotype associated) HFMD or herpangina in infants and young children without significant adverse reactions. The vaccine was trialled in children aged 6–35 months and as two 0.5 mL intramuscular injections 28 days apart. Long-term surveillance of the study participants is being performed to evaluate the longevity of serologic responses and vaccine protection and the need for booster injections. Vaccines for other virulent serotypes are also currently being researched.

IN A NUTSHELL

1. Enteroviruses are ubiquitous. Infections occur with seasonal periodicity in the summer and fall in temperate regions.
2. Majority of the infections are asymptomatic or cause self-limited minor illness.
3. Major outbreaks of illness occur with regular periodicity and may be associated with severe disease and fatality especially in the very young and immunocompromised.
4. Treatment is mainly supportive and symptomatic although IVIG and antiviral agents like pleconaril have been used anecdotally with some benefit in severe illness.

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Chapter 31.14

Herpes Simplex Infections

Niranjan Mohanty, Pradeep S

The family herpesviridae contain three subfamilies: (1) alphaherpesvirinae, (2) betaherpesvirinae and (3) gammaherpesvirinae. Herpes simplex virus (HSV) belongs to alphaherpesvirinae. Characteristics of the alphavirinae are short reproductive cycle, and efficient destruction of infected cells with release of viral progeny, rapid spread in culture, and latency in sensory ganglia. HSV-1 and HSV-2 belong to subfamily of alphaherpesvirinae. Eight herpesviruses are pathogenic to human, of which HSV-1 and HSV-2 are the major contributors. The word *herpes* means *to creep* in Greek. The earliest description of herpes as *fever blisters* was recorded by Hippocrates and Herodotus. In 17th century, Astruc described genital herpes lesion and in 1912, Gruter cultured HSV virus on rabbit cornea. Approximately one-third of children from lower socioeconomic population and about 20% from middle class have serologic evidence of HSV infection by 5 years of age. Direct person-to-person contact occurring in crowded living conditions partially accounts for these differences.

ETIOLOGY

The herpes viral particle has more than 30 structural proteins, icosahedral nucleocapsid with 162 capsomers and 100 nm in diameter. The viral particle is surrounded by an envelope, acquired via budding through inner lamella of nuclear envelope, multiple surface projections embedded in envelope. HSV-1 primary infection usually occurs in infancy or childhood, whereas primary infection with HSV-2 occurs after onset of sexual activity. Humans are the only known reservoir. Two types of HSV can be distinguished by restriction enzyme analysis of DNA, antigenic structure by Western blotting, and certain antigenic determinants. The viral glycoproteins are the major target for humoral immunity whereas other nonstructural proteins are important targets for cellular immunity. Several viral surface glycoproteins appear to be determinants of virulence. The glycoproteins like gB and gC mediate cellular attachment, gD is required for viral entry, gE for efficient expression of late genes and gI is a potent Fc receptor.

PATHOGENESIS

Infection of susceptible host occurs when the virus enters through the mucosa (oral mucosa, conjunctiva, genital mucosa) or break in keratinized epithelium. After entering the host virus replicates locally and enters nerve endings and replicates in sensory nerve ganglions. Then it moves through the neural arches which cause the characteristic herpetic lesion. Pathology of skin lesions shows sequential changes of balloon degeneration of infected cells, with condensation of nuclear chromatin, degeneration of cell nuclei and plasma membrane and formation of multinucleated giant cells. Mucosal membrane lesions are more prone for ulceration than skin lesions as thin layer of mucosal epithelium ruptures easily. When host is unable to control the viral replication (neonate or immunocompromised host), viremia occurs eventually leading to multiorgan involvement (**Flow chart 1**).

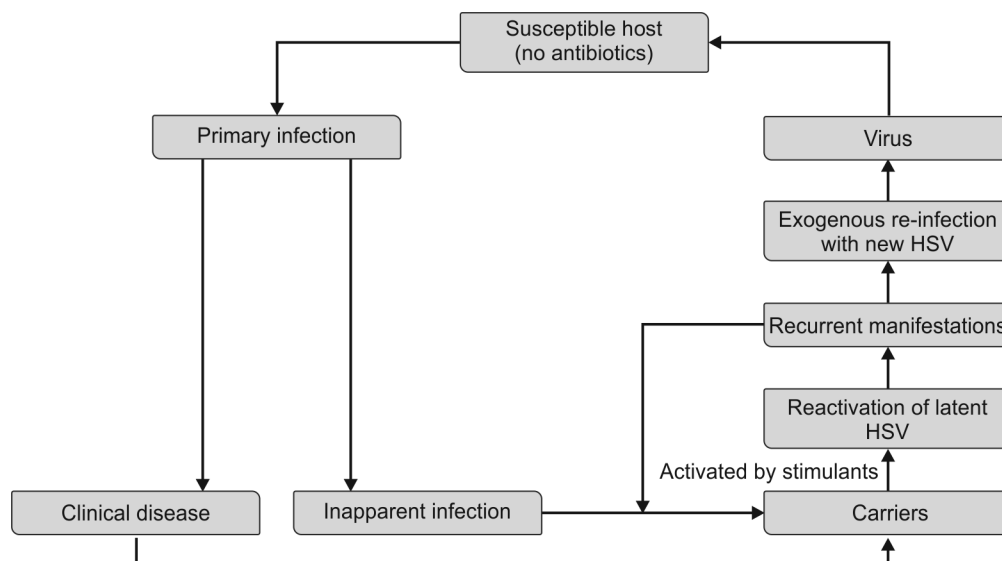
All herpesviruses have characteristic property of becoming latent after primary infection. Reactivation of HSV is regulated by the host immune factors, expression of cellular proteins in neuron and expression of HSV protein. A number of stimuli causing reactivation include manipulation of nerve roots, direct trauma to ganglia or skin/mucosa innervated by peripheral nerve, exposure to UV light, stress, hormonal changes, immunosuppressive agents and intercurrent infections. Recurrences are more common with HSV-1 and HSV-2, causing orolabial infections and genital infections, respectively. HSV infection can manifest as:

- **Primary infection** occurs in individuals who have not been previously infected by HSV-1 or HSV-2. The infections are severe due to lack of seropositivity.
- **Nonprimary infection** occurs in patients who have been exposed previously to either HSV-1 or HSV-2. The infections are not severe due to some level of cross protection.
- **Recurrent infection** During primary or non-primary infection, HSV establishes latent infection in regional sensory ganglion neurons. Usually they are asymptomatic.

CLINICAL FEATURES

Clinical manifestations depend on the type of infection (primary / nonprimary or recurrent), type of virus, port of entry, gestational age of neonate and maternal immunity. The typical lesions in primary infection manifest as small to large vesicles surrounded by an erythematous base, which eventually develops into ulcers and usually heals without scarring.

Flow chart 1 Host parasite interrelationship of herpes simplex virus (HSV)



Orolabial Infection

Primary infection classically presents at the age of 6 months to 5 years with extensive orolabial painful lesions (**Fig. 1**), high fever, irritability, drooling of saliva, refusal to feed and tender submandibular lymphadenopathy. Lesions heal without scarring in 6–10 days. Dehydration is the most common indication for hospitalization.

Reactivation lesions are usually asymptomatic, but the most commonly affected sites being outer edge of vermillion border of the lip and ophthalmic division of trigeminal nerve.

Cutaneous Herpes

Cutaneous herpes infections caused by direct contact and lesions develop at the port of entry. The manifestations range from severe pain to burning and itching mainly before the eruption of lesion. Herpetic whitlow refers to HSV infection of fingers and toes. Surgical intervention is contraindicated. HSV is most commonly recognized precipitating factor for recurrent erythema multiforme.

Genital Herpes (due to HSV-2)

Primary infection Nonspecific symptoms develop within 7 days of incubation. Lesions are distributed over the shaft of the penis in males and over labia, mons pubis, cervix and vaginal mucosa in females. Tender lymphadenopathy appears in 2nd and 3rd week of infection.

Nonprimary first episode Less severe lesions with more rapid healing and less severe complications.

Reactivation Usually asymptomatic, the carriers keep shedding the virus for long time.

Ocular Herpes

Infections occur through direct contact or peripartur route. Follicular conjunctivitis with pain, photophobia and tearing is followed by chemosis, periorbital edema and preauricular tender lymphadenopathy. Pathognomonic dendritic ulcers are the most common ocular manifestations of recurrent herpes.

CNS Herpes

Herpes simplex virus is the most common cause of severe, sporadic, fatal encephalitis world over. Encephalitis can be due to primary infection or more commonly due to reactivation. Beyond

neonatal period, HSV encephalitis is virtually caused by HSV-1. There occurs an acute necrotizing inflammation of temporal and frontal lobe and limbic system with hemorrhagic discharge into cerebrospinal fluid (CSF). HSV is the leading cause of recurrent aseptic meningitis (Mollaret's meningitis). CSF findings include RBC ($> 1,000/\text{mm}^3$), lymphoid pleocytosis ($> 1,000/\text{mm}^3$) and protein concentration which increase after the first week up to 500–1,200 mg/dL. Electroencephalogram (EEG) shows focal spike and slow wave abnormality with characteristic findings of paroxysmal lateralizing epileptiform discharges (PLEDs). The disease has very poor prognosis with subsequent death occurring in 75% of cases.

Herpes in Immunocompromised Hosts

In immunocompromised hosts, HSV infection is a frequent source of morbidity and the risk of severity parallels the extent of compromise in cellular immune response. Mucocutaneous infections (mucositis and esophagitis) are most common and may cause ulcerations deep into the tissue and necrosis. The healing takes an average of 6 weeks. Other infections include tracheobronchitis, pneumonitis and hepatitis. Viremia can lead to disseminated sepsis, shock and disseminated intravascular coagulation (DIC).

Neonatal Herpes

The estimated prevalence of neonatal herpes is 1 in 3,000–5,000 live births. Around 70–80% neonatal HSV infections are due to HSV-2. The infection occurs more commonly in infants born to mother with recent infection rather than due to recurrent genital herpes. HSV infection is acquired during in utero, peripartum or postpartum, often during delivery. Risk of transmission is high with mother having primary infection or with intrapartum interventions and baby with low gestational age.

Patterns of Neonatal Herpes

Neonatal HSV infection manifests in three ways with almost equal proportions having considerable clinical overlap: (1) *Skin, eye and mouth* (SEM) form is never asymptomatic. They present with skin lesions from birth or typically manifests within 2 weeks of life (**Fig. 2**). Usually the skin lesions appear at the site of trauma as vesicles. Any vesicle on a neonate HSV infection should be considered. The common ocular lesion is keratoconjunctivitis which can progress to chorioretinitis, cataract and retinal

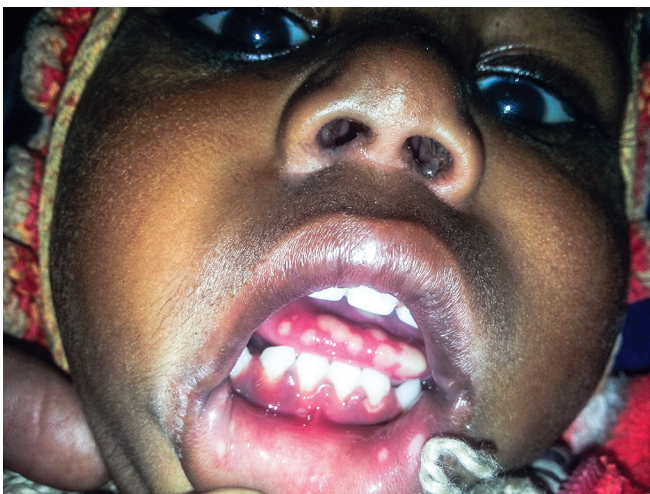


Figure 1 Herpetic gingivostomatitis
Source: Dr Arun Shah, Muzaffarpur, Bihar, India.



Figure 2 A 10-month-old native American infant presented with herpes simplex (HSV-2) skin lesions on her face, torso, arm and leg
Source: JD Millar, Public Health Image Library (PHIL), CDC, USA.

detachment despite therapy. Outcome of SEM is excellent if treated at early stage. (2) *Central nervous system (CNS) infection* with or without skin lesions can present as seizures (usually focal and difficult to control), lethargy and irritability with onset around 14–21 days of life. (3) *Disseminated form* presents as shock, hepatomegaly, jaundice, bleeding and respiratory distress within 5–11 days of life. Nearly 70% of cases demonstrate skin lesion during the illness which are often absent at the onset of symptoms.

DIFFERENTIAL DIAGNOSIS

Orolabial infections Viral or bacterial pharyngitis, herpangina, acute membranous tonsillitis, thrush.

Cutaneous infections Eczema of secondary bacterial infection and cellulitis, varicella, eczema vaccinatum.

Genital infections Chlamydial infection, gonorrheal and monilial vulvovaginitis, impetigo, ammoniacal dermatitis with secondary infection.

Ocular infections Any conditions causing conjunctivitis and/or corneal ulcer.

CNS infections Viral meningoencephalitis, cerebral malaria, meningitis, vascular diseases, brain abscess.

Neonatal disseminated form Neonatal sepsis, enteroviral infection, pneumonia, meningitis.

DIAGNOSIS

Cytopathological effects of HSV and isolation on viral culture are the gold standard for diagnosing herpes infection. Fluorescent antibody staining and enzyme immune assay are used for culture confirmation. Isolation of virus or viral DNA by polymerase

chain reaction (PCR) is diagnostic method of choice. Histological examination and viral culture of brain tissue specimen are the most definitive method of confirming the diagnosis of encephalitis. Immunoglobulin M (IgM) antibody estimation is unreliable, but IgG estimation in acute and convalescent serum showing fourfold rise is significant. Presence of type specific antibody to HSV-2 indicates anogenital infection. Polymorphonuclear leukocytosis occurs in mucocutaneous infection and in disseminated infection, thrombocytopenia, abnormal coagulating profile and raised liver enzymes are documented. Bedside investigation like Tzanck smear can be used to demonstrate the multinucleate giant cell.

TREATMENT

Treatment of herpes simplex infections is shown in **Tables 1** and **2**.

PREVENTION

Horizontal transmission is prevented by isolating the individual till the viral shedding has stopped. Vertical transmission can be prevented by treating the mother during pregnancy, delivery by cesarean within 4–6 hours of rupture of membranes. There are no clear guidelines to start of prophylactic acyclovir in neonates.

PROGNOSIS

Most of the herpes infections are self-limiting, recurrent orofacial herpes can lead to facial scarring. Life-threatening complications can occur in neonates and immunocompromised children causing mortality. Mortality without treatment can go up to 90% in disseminated form and 50% due to encephalitic form. Severe morbid states like postencephalitis sequel, corneal scarring and blindness (neonatal herpes: SEM form) are serious concern for parents and caregivers.

Table 1 Choice of antiviral drug in herpes simplex infections

Clinical syndrome of HSV infection	Agent of choice	Alternative agent
Neonatal herpes	Acyclovir (IV)	
HSV encephalitis	Acyclovir (IV)	
HSV gingivostomatitis	Acyclovir (PO)	Acyclovir (IV)
1st episode genital infection	Acyclovir (PO)	Valacyclovir, famciclovir Acyclovir (IV) (severe disease)
Recurrent genital herpes	Acyclovir (PO)	Valacyclovir Famciclovir
Suppression of genital herpes	Acyclovir (PO)	Valacyclovir Famciclovir
Whitlow	Acyclovir (PO)	
Eczema herpeticum	Acyclovir (PO)	Acyclovir (IV) (severe disease)
Mucocutaneous infection in immunocompromised host (mild)	Acyclovir (IV)	Acyclovir (PO) (if outpatient therapy acceptable)
Mucocutaneous infection in immunocompromised host (moderate to severe)	Acyclovir (IV)	
Prophylaxis in bone marrow transplant recipients	Acyclovir (IV)	Valacyclovir, famciclovir
Acyclovir-resistant HSV	Foscarnet	Cidofovir
Keratitis or keratoconjunctivitis	Trifluridine	Vidarabine

Note: Valacyclovir, a prodrug of acyclovir, and famciclovir, a prodrug of penciclovir.

Table 2 Dose and duration of treatment of herpes simplex infections

Type of infection	drug	Dose	Duration	Comments
Gingivostomatitis	Acyclovir	15 mg/kg/dose (max 1 g/day) oral	5/day x 7 days	If started within 72 hours, severity reduces
Herpes labialis	Acyclovir	200–400 mg/dose oral	5/day x 5 days	Severe infection in burn cases, acyclovir IV 10–20 mg/kg 8 hourly
Frequent and severe recurrence	Acyclovir	200–400 mg/dose oral	2/day, long-term daily usage	
	Valacyclovir	500 mg/dose oral	Once daily, long-term daily usage	
Herpes gladiatorum	Acyclovir	200 mg/dose oral	5/day x 7–10 days	
Genital herpes	Acyclovir (children)	10–20 mg/kg/dose oral	4/day x 7–10 days	Oral is as efficacious as IV therapy. To start within 6 days of onset, to reduce severity, shortens the duration of illness and viral shedding
Adolescents	Acyclovir	400 mg oral	3/day x 7–10 days	
	Famciclovir	750 mg oral	3/day x 7–10 days	
	Valacyclovir	1,000 mg oral	2/day x 7–10 days	
Recurrent infections	Acyclovir	800 mg oral	3/day x 2 days	Based on severity and frequency, psychological impact and transmission to partner
Episodic therapy	Famciclovir	500 mg oral	2/day x 3 days	
	Valacyclovir	100 mg oral	2 times for 1 day	
Long-term therapy	Acyclovir	400 mg oral	2/day for 1 year	For patients with frequent genital HSV, to prevent outbreak, improves quality of life, decreases the risk of sexual transmission
	Famciclovir	250 mg oral	2/day	
	Valacyclovir	500–1,000 mg oral	4/day	
CNS infections (other than neonates)	Acyclovir	10–20 mg/kg/dose IV	3/day x 14–21 days	Other treatment raised ICT, respiratory compromise and seizures
Immunocompromised persons	Acyclovir	5–10 mg/kg/dose IV Severe mucocutaneous, disseminated HSV	3/day, until the resolution of infection is evident	Less severe infections treated with oral acyclovir, famciclovir, valacyclovir
Neonatal herpes	Acyclovir	10–20 mg/kg/dose IV	3/day x 14 for SEM form and 21 days for CNS or disseminated form	

Note: Acyclovir-resistant cases treated with high dose of acyclovir infusion at the rate of 1.5–2 mg/kg/h or IV foscarnet or IV cidofovir.

IN A NUTSHELL

1. Of eight herpesviruses pathogenic to human, HSV-1 and HSV-2 are more prevalent, mostly in children under 5 years.
2. Herpes simplex virus is a DNA virus with short reproductive cycle and latency in the sensory ganglion.
3. Herpes simplex virus infection could be primary, nonprimary and recurrent. Various stimuli can reactivate this infection.
4. Primary infection often leads to serious manifestations, while nonprimary and recurrent infection remain asymptomatic.
5. HSV-1 and HSV-2 predominantly cause orolabial and genital lesions respectively.
6. Neonates and immunocompromised hosts experience more severe illness.
7. Isolation of virus or viral DNA is the diagnostic method of choice.
8. Acyclovir is the drug of choice in appropriate route, dosage and duration.

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Chapter 31.15

Influenza

Sonal Kansra, Alison Scott

Globally, diseases caused by influenza viruses result in significant morbidity and utilization of health care services. The potential for rapid spread across political and geographic borders makes this an important public health priority. During epidemics, the highest rates of influenza infection occur in preschool children. Children are also the main disseminators of influenza viruses in the community. Children with underlying chronic conditions are especially vulnerable and likely to need hospitalization. Symptoms are nonspecific, the diagnosis largely clinical and treatment is mainly supportive.

EPIDEMIOLOGY

Influenza viruses have a global distribution. In temperate climates, seasonal epidemics occur mainly during winter while in tropical regions, influenza may occur throughout the year, causing outbreaks more irregularly. Data from the WHO Global Influenza Surveillance Network in India shows a trend of influenza peaks in the month of June to September which is related with the monsoon across major parts of the country. The incidence of influenza illness as well as influenza-associated acute lower respiratory tract infection (LRI) is three times higher in developing countries as compared to the industrialized countries. Under-5 children have the highest rates of influenza infection. A recent epidemiological study estimated incidence of influenza episodes to be 154/1,000/year in under-5 children in developing countries. The rate of influenza-associated acute LRI and influenza-related severe LRI were estimated at 35 and 2/1,000/year in this age group, respectively. The same study calculated the incidence of influenza-related severe acute LRI to be 1/1,000/year giving a population estimate of 256,000 new episodes per year in 2008.

ETIOPATHOGENESIS

Influenza viruses (**Fig. 1**) are RNA viruses belonging to the Orthomyxovirus family. These are of three types: (1) A, (2) B and (3) C. Type A infects humans and other species (waterfowl is thought to be the natural reservoir of influenza) whereas B infects mainly humans. The type A is further subtyped based on surface antigens—hemagglutinin (HA or H) and neuraminidase (NA or N). Types A and B are responsible for most clinical cases. Cases of influenza A occur with seasonal predilection in the cold countries whereas influenza B epidemics usually occur every few years. Influenza viruses are constantly evolving and change in two different ways—(1) antigenic drift and (2) antigenic shift.

Antigenic drift Small, gradual changes in antibody-binding sites (HA and NA) of a virus that may make it resistant to antibodies formed against earlier strains. This type of rearrangement is seen in both type A and type B viruses.

Antigenic shift An abrupt major change that produces a novel influenza A virus subtype that had not previously circulated. Antigenic shift is largely a characteristic of influenza A virus and may lead to epidemics or even pandemics because immunity from the previous virus may not protect completely against the new subtype, meaning the population may have little or no immunity.

Over the last 100 years, there have been five influenza pandemics due to emergence of novel viruses. Most recently a novel H1N1 human-swine-avian reassortant virus in 2009 in North America started a new pandemic which quickly spread globally.

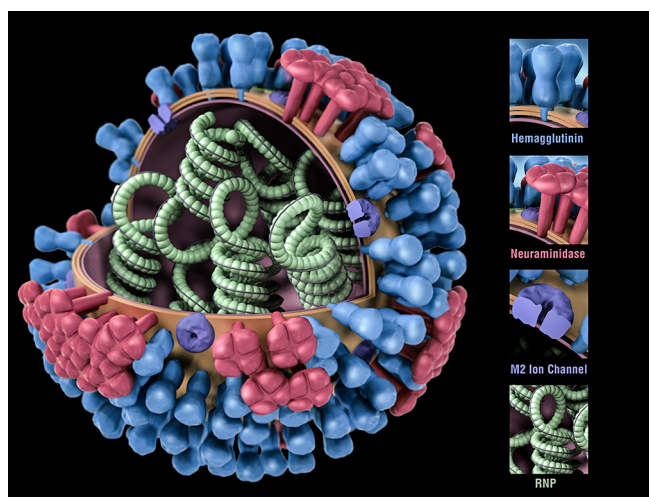


Figure 1 Influenza virus. A three-dimensional (3D) graphical representation of a generic influenza virion's ultrastructure, and is not specific to a seasonal, avian or 2009 H1N1 virus. In this particular view, a portion of the virion's protein coat or *capsid* has been cut away, revealing its inner nucleic acid core proteins. Note the key to the right identifying the virion's protein constituents

Source: Public Health Image Library (PHIL), CDC, USA. Illustrator: Dan Higgins.

CLINICAL FEATURES

Incubation period of influenza is 1–4 days. The child may remain infective for 10 or more days after illness onset. The amount of virus shed is thought to decrease rapidly after 3–5 days. Severely immunocompromised persons shed virus for weeks to months. The spread is usually via large particle droplets (aerosols) but can also be spread via surface contact. Transmission requires close contact as droplets do not remain suspended in air for a long time and travel only a short distance (< 1 m) in the air. Viruses attach to sialic acid containing receptors on the cell surface of respiratory mucosa.

About 30–50% of influenza may be asymptomatic; however, this depends on the characteristics of the influenza virus strain. Clinically influenza is characterized by an acute onset of fever, chills, myalgia, headache, malaise and fatigue. Dry cough, sore throat and nasal congestion may be present. The symptoms are fairly unpleasant but self-limiting. Uncomplicated influenza illness typically resolves after 3–7 days for the majority of persons, although cough and malaise can persist for greater than 2 weeks. Younger children are less likely to report typical influenza symptoms of cough and malaise. They more frequently present with signs and symptoms of croup, bronchiolitis or sepsis (with high temperatures).

In the most recent pandemic of influenza, a large proportion of patients also had gastrointestinal symptoms. Neurological symptoms: encephalopathy, transverse myelitis and Reye syndrome have been uncommonly reported. Cardiac involvement from myocarditis and pericarditis is also described. Although primary influenza pneumonia is a rare complication that may occur at any age and carries a high case fatality rate, it was seen more frequently during the 2009 pandemic and the following influenza season. Secondary bacterial infection, especially with *Staphylococcus aureus* or *Streptococcus pneumoniae*, is a significant concern. This may lead to acute otitis media (almost 40% of children under-3) or bacterial pneumonia especially in young children. Sinusitis and tracheitis may be seen. Risk of serious illness from infection is highest in children less than 6 months of age and children with

pre-existing conditions such as cardiac, neurological disease or immunodeficiency. Children with asthma have a higher rate of hospitalization with influenza.

DIAGNOSIS

Diagnosis remains largely clinical. Symptoms are nonspecific and overlap with other illnesses. Viral cultures, polymerase chain reaction (PCR) and antigen detection usually in nasal or throat swabs can be used to aid clinical diagnosis although the latter two methods cannot distinguish recent from current infection.

TREATMENT

The mainstay of treatment for influenza has been largely symptomatic until recently. Antipyretics, analgesia and adequate oral fluids are recommended but will not reduce the duration of the illness. The pandemic of H1N1 in 2009 brought the use of antiviral agents into public awareness and governments have spent significant amounts of health care budgets stockpiling these agents. The most commonly used agent is oseltamivir (Tamiflu) which is a NA inhibitor, reducing the virus' ability to break through cell walls and infect other cells and replicate.

Previous policies regarding the use of antiviral agents were developed based on studies, which were manufacturer led, demonstrating benefit with oseltamivir to reduce complications and transmission from influenza. A recent Cochrane review (2014) assessed the risk of publication bias by obtaining all relevant full clinical study reports relating to studies in oseltamivir and found that the use of the drug in children reduced symptom duration (but not in asthmatic children); did not affect rates of hospital admission; did not affect incidence of pneumonia; and reduced symptomatic influenza when used prophylactically. The reviewers express significant concerns regarding the likely mode of action, the size of the effects and the incidence of side effects including nausea, vomiting, headaches and renal and psychiatric syndromes. Guidance on the use of oseltamivir may change in response to these findings and readers are advised to review the most current guidelines.

PREVENTION

Preventing Spread

The most important way to stop flu spreading is good respiratory and hand hygiene. Regular washing of hands and cleansing of work surfaces is important. The most benefit from preventing respiratory virus spread from hygienic measures is in younger children. This is however quite difficult to achieve in children due to their frequent and extensive social contact and long duration of viral shedding. The use of isolation and physical barriers in the form of masks, gowns and gloves, may contain influenza epidemics, or the presence of disease on hospital wards. Global measures, such as screening at entry ports, have not been scrutinized closely but are thought to lead to a nonsignificant marginal delay in spread.

Vaccines

The World Health Organization (WHO) believes that vaccination is the principle measure for preventing influenza and reducing its impact. Influenza vaccination has existed since the 1960s and the WHO has produced guidance regarding vaccine composition since 1973. The WHO recommends vaccination strains of influenza following review of epidemiological data. Seasonal influenza vaccines are usually trivalent, and contain a mixture of the strains predicted to be present in the coming influenza season. This is usually two influenza A strains and one of influenza B. Monovalent vaccines have been developed for pandemic strains. Quadrivalent vaccine with a second influenza B virus in addition to the viruses in the conventional trivalent vaccines has been made available since 2013.

The vaccine is produced through a process known as reassortment. This is the method of combining a strain with the predicted combination of HA and NA antigens (strain 1) with a harmless strain that will grow well in an egg (strain 2). Following injection into a fertilized chicken egg, multiple genetic combinations are created and analyzed, leading to the selection of the strain with the combination of appropriate antigens and the ability to efficiently grow in eggs for development. Influenza vaccination can be both inactivated and injected and attenuated which is delivered nasally.

The WHO recommends vaccination in the following groups: nursing home residents; those with chronic medical conditions; the elderly and others, including health care workers and children aged 6 months to 2 years. In India, the Indian Academy of Pediatrics Committee on Immunization (IAPCOI) recommends influenza vaccine in following groups:

- Congenital or acquired immunodeficiency
- Chronic cardiac, pulmonary, hematologic, renal, liver disease and diabetes mellitus
- Children on long-term aspirin therapy
- Any neurologic disease that might cause respiratory compromise or impair ability to clear secretions
- Asthma requiring oral steroids.

Vaccines should be stored at 2–8°C and never be frozen. The trivalent vaccines are licensed for use in children aged 6 months and older. Inactivated vaccines should be used in the at risk groups. As cases in tropical countries occur year-round vaccination should be given as soon as new vaccine becomes available. When vaccines are used for the first time in children aged 6 months to 9 years, two doses are recommended. After 9 years, a single dose only may be needed. Readers are referred to the IAP immunization guidebook for a detailed discussion about vaccinations.

Live attenuated influenza vaccination has an efficacy of up to 80% and around 33% effectiveness in preventing cases of disease in children over 2 years of age. This is lower in the inactivated vaccination (approximately 59% and 36%, respectively). Narcolepsy and febrile convulsions have been associated with some strains of the vaccination in children.

AVIAN INFLUENZA

Avian influenza, commonly referred to as bird flu, is a zoonotic disease, i.e., human infection with a viral strain which normally affects birds. However, there is a potential for human-to-human transmission. A highly pathogenic H5N1 strain of influenza has been responsible for outbreaks in birds (and some human cases) since 1997. This originated in Southeast Asia and spread westward. H5N1 is a fast mutating strain and is now panzootic (a disease affecting animals of many species over a wide area). Numerous countries across the globe have reported this strain in wild as well as farm birds. There have been further reports of avian influenza H5N1 in humans since 2003 prompting concerns that conditions are suitable for emergence of a pandemic strain. Two features of avian influenza H5N1 outbreaks are striking: (1) the predominance of children and young adults and (2) the high mortality rate.

In late March–April 2013, human cases of severe pneumonia caused by novel avian influenza A H7N9 infection in China were reported to the WHO. Most of these infections are believed to result from exposure to infected poultry or contaminated environments. Like H5N1 most affected individuals have had severe disease and the strain has been fatal in almost a third. At present, the WHO does not recommend antiviral chemoprophylaxis following exposure to H7N9 virus (exposure to live poultry environments contaminated with H7N9 or patients with H7N9 infection). Symptomatic individuals with exposure to H7N9 virus should receive prompt antiviral treatment with

a NA inhibitor. Prophylaxis may be considered in at risk (e.g., immunodeficient) asymptomatic individuals and health care workers with unprotected exposure.

IN A NUTSHELL

1. Influenza viruses are a significant cause of illness and hospitalization in children.
2. Younger children and those with chronic medical conditions are at increased risk of hospitalization from infection.
3. Influenza viruses are constantly evolving and this produces a challenge for vaccination programs and individual immunity.
4. Spread is by particle droplets and surface contact.
5. Cases are usually mild and can be asymptomatic. Secondary bacterial infection can cause serious illness such as pneumonia or otitis media.
6. Effective hand hygiene and contact restriction techniques using barrier methods can limit the spread of the virus.
7. Vaccines are based on recommended strains for an approaching season by the WHO. Trivalent inactivated vaccines are currently recommended by IAP in the at risk groups.
8. Antiviral agents can reduce symptom duration. Their widespread use and the supporting evidence have been questioned.

MORE ON THIS TOPIC

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Chapter 31.16

Dengue

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Dengue infection results in an acute febrile illness, caused by 4 closely related virus serotypes of the genus *Flavivirus*, family *Flaviviridae*. Dengue virus is transmitted to humans mainly by the *Aedes aegypti* mosquito. The disease is characterized by a biphasic fever, and may be associated with hemorrhagic manifestations. In 10–20% cases, the patient develops shock because of plasma leakage into the third space. Worldwide, children younger than 15 years comprise 90% of patients with dengue fever.

CLINICAL SPECTRUM

Dengue virus infection may be asymptomatic, lead to a benign illness, or present with severe manifestations. The World Health Organization (WHO) in 1997 classified symptomatic dengue virus infections in the following groups:

1. Undifferentiated dengue fever
2. Dengue fever. Defined as presence of fever of 2–7 days duration with any two of the following—myalgia, retro-orbital pain, headache, rash, arthralgia
3. Dengue hemorrhagic fever (DHF). A patient is classified as DHF if following four criteria were met: (i) fever or history of fever in last 2–7 days; (ii) bleeding tendencies—positive tourniquet test, petechiae, purpura, mucosal bleeds; (iii) thrombocytopenia—platelet count less than $100,000/\text{mm}^3$; and (iv) hemoconcentration [defined as $> 20\%$ rise in hematocrit (Hct)] or evidence of plasma leakage—pleural effusion, ascites or hypoproteinemia. The DHF was further graded in four stages (**Box 1**)
4. Dengue shock syndrome (DSS). All of above criteria plus hypotension.

BOX 1 Grading of dengue hemorrhagic fever (WHO, 1997)

Grade I: Fever, nonspecific complaints, positive tourniquet test, no spontaneous bleeds
Grade II: Spontaneous bleeds in addition to signs and symptoms of grade I
Grade III: Circulatory failure—cold clammy extremities, hypotension
Grade IV: Profound shock

Later, it was realized that this classification was at times difficult to apply in clinical settings, was not able to categorize all patients with dengue, and was missing out cases with severe dengue. Also, dengue fever and DHF may not be continuum of same disease and may exist as separate clinical conditions. WHO thus proposed a new classification for severity of dengue fever in 2009.

The new WHO classification has three severity categories: (1) dengue fever; (2) dengue fever with *warning signs*; and (3) severe dengue (**Fig. 1**). It is important to note that children without warning signs can also develop severe dengue.

- *Nonsevere manifestations* consist of a biphasic fever, generalized bodyache, rash, and a positive *tourniquet test*. These may or may not be associated with warning signs.
- *Warning signs* should be detected by close observation of the patient, so as to institute early and aggressive therapy. These include (1) abdominal pain or tenderness; (2) persistent vomiting; (3) clinical fluid accumulation (edema, pleural effusion, ascites); (4) mucosal bleeds; (5) hepatomegaly by greater than 2 cm; and (6) hemoconcentration as evidenced by increasing Hct with concomitant and rapid fall in platelet count.
- *Severe manifestations* include (1) severe hemorrhage; (2) profound shock; and (3) multisystem involvement. Presence of any one of these three criteria is sufficient for making a diagnosis of severe dengue infection.

Expanded dengue syndrome is a term introduced in 2011 which refers to unusual and severe involvement of liver, kidney, brain, or heart in association with dengue.

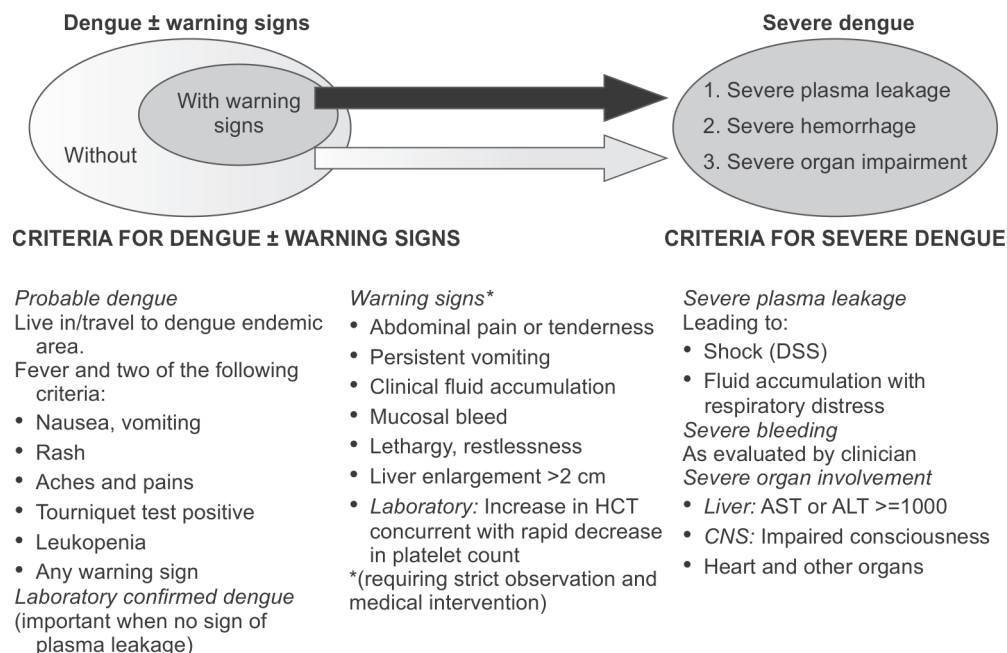


Figure 1 Suggested dengue case classification and levels of severity
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GEOGRAPHICAL DISTRIBUTION

Global

Dengue fever is known in the tropical Southeast Asia and Western Pacific for more than a century. The hemorrhagic form was first recognized in Philippines in 1953. Subsequently DHF was recognized in Thailand, India, Malaysia, Singapore, and Vietnam. In 1978, a big outbreak was reported from China resulting in 22,122 cases. In 1981, a large epidemic occurred in Cuba resulting in nearly 0.35 million cases of dengue fever. Out of these, 24,000 had DHF and 10,000 had DSS. Dengue has also been noticed in temperate regions of North America, Africa, and Mediterranean Europe.

As per current estimates, at least 100 countries are endemic for DHF and about 40% of the world populations (2.5 billion people) are at risk in tropics and subtropics. In 2010, 1.6 million cases of dengue were reported in the Americas alone, of which 49,000 cases were severe dengue. Recently, dengue has also been reported from Costa Rica, Mexico, France, Croatia and Portugal. Incidence of dengue infections annually has almost doubled from 50 million to 96 million (2010) in last few years.

India

India alone accounted for almost 34% of global dengue burden by 2010. Disease is prevalent throughout India in most of the metropolitan cities and towns. Outbreaks have also been reported from rural areas of Haryana, Maharashtra and Karnataka. During 1996, a severe outbreak of dengue/DHF occurred in Delhi wherein about 10,252 cases and 423 deaths were reported. In 2006, India witnessed another outbreak with 12,317 cases and 184 deaths in 21 states. The initial epidemics in India were due to serotype 2 or 4. The dengue serotype 1 was seen as predominant serotype in Delhi during 2007–2010. Concurrent infection of chikungunya and dengue serotype 2 has been reported from Vellore and Delhi.

ETIOLOGY

Dengue virus has at least 4 serotypes (1, 2, 3, and 4). These are antigenically very similar but do not offer a complete cross-protection after infection by either one of them. Infections in human by a serotype will produce lifelong immunity against reinfection by the same serotype. Subsequent infection (secondary infection) by another serotype results in severe dengue. The severity of epidemics caused by serotype 1 has been reported to be maximum followed by type 2 and 3.

EPIDEMIOLOGY

Vector

Aedes aegypti is the vector for dengue virus. Female mosquito bites the man during daytime. After feeding on a person with viremia, the female mosquito can transmit dengue immediately or after a period of 10–14 days (*extrinsic incubation period*). The extrinsic incubation period is a critical factor in successful transmission of the disease. A lower environmental temperature increases the extrinsic incubation period, which in turn, decreases the transmission. Once the mosquito becomes infective, it remains so till it dies.

The flight range of an adult *A. aegypti* mosquito is not more than 25–50 m in an urban environment. However, the vector can be transported by water, land, and air travel contributing to the transmission. For dengue transmission, the number of infected female mosquitoes per house is important. Usually this number is small, and in an Indian epidemic it was observed to be just 1 per household (*house index*). The minimum vector density, below which the dengue transmission ceases, is not known. The *A. aegypti* mosquito breeding is not necessarily related to the

ambient temperature. The mosquito has been found at altitudes as high as 2,200 m above the sea level. Vectors must survive longer than the sum of the initial nonfeeding period after birth (usually 2 days) and the extrinsic incubation period to be able to infect another human. Longevity under natural conditions ranges from 8 days to 42 days. The eggs of *A. aegypti* can survive without water for an year.

Host

People at all ages are susceptible to dengue. In Asians, disease is more severe in children. This is in contrast to America where infection mainly occurs in adults which is generally mild. Severe dengue occurs at high frequency in (1) infants; and (2) children having experienced a previous dengue infection. Other factors associated with increase host susceptibilities to severe disease include bronchial asthma; human immunodeficiency virus (HIV); certain human leukocyte antigen (HLA) types—HLA I (A04, A24, B0, B46), HLA II (DR1, DR4, DQ); polymorphisms in tumor necrosis factor-alpha (TNF- α); transforming growth factor-beta (TGF- β); vitamin D receptors; glucose-6-phosphate dehydrogenase deficiency and mutations in mannose-binding lectin-2 gene.

Environmental Factors

In many tropical countries, a positive association between rainfall or larval density and dengue incidence has been documented. The vector survives best at temperature 16–30°C and humidity of 60–80%. However, dengue epidemics have also been recorded in those areas where rainfall is unusually low. The transmission occurs only if the ambient temperature is above 16°C. Therefore, the transmission tends to decline when winter approaches. This is due to prolongation of extrinsic incubation period beyond the longevity of mosquito.

Transmission Risk Factors

When a member of a household is infected with dengue, other family members are at risk. Dengue spread is facilitated in any vector infested place where people congregate, such as schools, temples, cinema halls, offices, hospitals, factories, etc. In urban areas, the movement of infected people accounts for spread of virus than the movement of *Aedes* mosquito.

In utero transmission Dengue infection of pregnant women may result in passive transfer of antidengue immunoglobulin G (IgG) to the fetus or a congenital infection. These infants with maternal antibody are at a higher risk of developing severe dengue and many develop DHF during primary exposure.

PATHOGENESIS

Dengue virus infects the peripheral blood mononuclear cells within a few days of infective mosquito bite. Two patterns of immune response follow: (1) *primary* and (2) *secondary (anamnestic)*. Persons never previously infected with a flavivirus, nor immunized with a flavivirus vaccine (e.g., yellow fever, Japanese encephalitis), mount a primary IgM antibody response when infected with dengue virus, appearing within 2–3 days of defervescence and peaking at 2 weeks after the onset of symptoms. Antidengue IgG appears afterwards. Individuals with immunity due to previous flavivirus infection or immunization mount a secondary (anamnestic) antibody response when infected with dengue virus. In secondary flavivirus infections, which account for most cases of severe dengue, the dominant immunoglobulin is IgG; the levels of IgM being much lower.

Antibody against a strain of dengue virus does not protect from a different strain of virus. Rather, it may increase its capacity to multiply in human monocytes. The infected monocytes result in

activation of cross-reactive CD4+ and CD8+ cytotoxic lymphocytes. Cytotoxic lymphocytes mediate release of cytokines resulting in plasma leakage and hemorrhage.

PATHOPHYSIOLOGY

Two main pathophysiological changes occur in dengue. These are (1) *increased vascular permeability*, resulting in loss of plasma from the vascular compartment, hemoconcentration, low pulse pressure, and other signs of shock; and (2) disorder in the hemostasis involving thrombocytopenia, vascular changes, and coagulopathy.

Secondary dengue infection results in formation of immune complexes and activation of complement system. TNF- α , interferon, and interleukin-2 are elevated, and C1q, C3-C8, are depressed. As a result, vasoactive amines are released from the platelets. These cause massive release of water, electrolytes, and plasma proteins from the blood vessels and lead to hypovolemic shock. Increased vascular permeability is mediated through the nitric oxide pathway.

Platelet defects are both quantitative and qualitative. Thus, a patient with a normal platelet count may still have a prolonged bleeding time. Maculopapular and petechial rashes are present. In these lesions, dengue antigen, IgM and complement (C3) have been observed.

It may be noted that virus is usually not detectable in blood once shock manifests, though viral replication occurs in various organs.

CLINICAL FEATURES

Dengue infections have a wide clinical presentation. Following an incubation period of 3–7 days, the illness is characterized by three distinct phases: (1) febrile phase, (2) critical phase, and (3) phase of recovery.

Febrile Phase

This phase is characterized by a high-grade fever up to 104°F, abrupt in onset. Fever remains at the peak for 48–72 hours before it starts declining. It is accompanied with nonspecific constitutional symptoms such as generalized myalgia, body ache, anorexia, nausea, vomiting, and headache. Parents may notice an erythematous rash, especially over the extremities. Some children may have associated sore throat, or arthralgia. These features, by themselves, are however not sufficient enough to arrive at a diagnosis of dengue fever. Dengue should be strongly suspected, if above features are associated with mild hemorrhagic manifestations including petechial hemorrhages, mucosal bleeds, or a positive tourniquet test. Presence of tender hepatomegaly (without obvious icterus) strongly favors possibility of dengue infection. The febrile phase lasts for 2–3 days.

Complication High fever in this phase can cause dehydration, febrile delirium, and febrile seizures in children less than 5 years of age.

Critical Phase

Onset of the critical phase is closely linked to the time of defervescence that occurs by third day of illness. All children in defervescence phase need to be closely monitored for the *warning signs* as described earlier. Those manifesting with one or more of these signs are likely to enter the critical phase. Not all children with dengue infection enter this phase. Many children improve progressively after defervescence (nonsevere dengue).

Critical phase is characterized by an increase in capillary permeability. This is preceded by a fall in the platelet count. Increased capillary permeability results in leakage of plasma into

the third space. Clinically, this manifests as polyserositis, i.e., pleural effusion and ascites. Plasma leakage from the intravascular compartment into the third space results in hemoconcentration in the vascular bed, reflected by a rising Hct. Increase in Hct is directly proportional to the volume of plasma lost from the vascular compartment.

Epigastric discomfort, tenderness at right costal margin, and generalized abdominal pain are common. Liver becomes palpable. Petechiae may be present over extremities, axillae, face, and palate.

Leakage of a significant volume of plasma leads to hypovolemia, hypoperfusion, and shock. Hypoperfusion may result in multiple end-organ impairment, metabolic acidosis, and disseminated intravascular coagulation (DIC). Consumption coagulopathy results in hemorrhage that may cause a fall in Hct. End-organ impairment manifests with hepatitis, myocarditis, or encephalitis. Children developing profound shock, severe hemorrhage, or multisystem involvement are at higher risk of mortality and thus are said to be having *severe dengue infection*. These children need aggressive management. This phase lasts for 48 hours.

Recovery Phase (Plasma Reabsorption Phase)

Plasma starts coming back to the intravascular compartment, provided the patient survives the critical phase of plasma leakage and shock. Onset of this phase is characterized by an improvement in general well-being and appetite. Urine output improves, and pain abdomen subsides. Though this is the phase of improvement, child should be monitored carefully for hypervolemia. Reabsorption of leaked plasma plus administration of excess intravenous (IV) fluid may result in fluid overload, pulmonary edema, and congestive heart failure, manifesting as dyspnea, tachycardia, and raised jugular venous pressure. Cardiovascular manifestations (bradycardia, arrhythmias) are also reported during this phase. Hct value either normalizes or may show a decline below normal. Platelet count starts improving. This phase lasts for 48–72 hours. Thus, most patients with dengue fever run a typical course of disease lasting from 7 days to 10 days (**Fig. 2**).

Severe Dengue

Children and adolescents with severe dengue have a more protracted course and recovery may take 10–14 days. Dengue shock is characterized by a narrow pulse pressure less than or equal to 20 mm Hg, cold extremities, delayed capillary refill time, weak

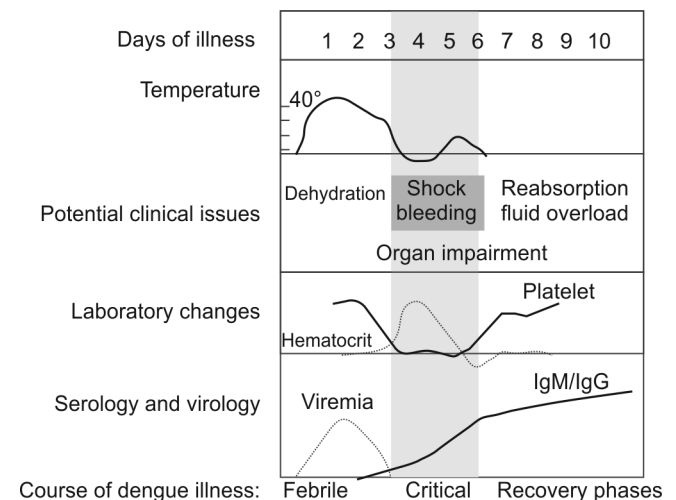


Figure 2 The course of dengue illness
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pulse, and tachycardia. Skin becomes cool, blotchy, congested. Typically, consciousness is not altered. Major bleeding can occur from gastrointestinal tract or brain. Organ impairment manifests as hepatic failure, renal failure, myocarditis, or encephalopathy. Atypical manifestations include acute inflammatory colitis, uveitis, myositis, Guillain-Barré syndrome, and Kawasaki disease.

DIAGNOSIS

Hematological Tests

The clinical diagnosis is corroborated by raised hematocrit (Hct) and thrombocytopenia:

- An Hct level rise of greater than 20% is a sign of hemoconcentration and precedes shock. The Hct level should be monitored at least every 24 hours to facilitate early recognition of *warning signs* and every 3–4 hours in *Severe dengue*.
- Thrombocytopenia occurs in up to 50% of children with dengue. Platelet counts of less than 100,000 cells/ μ L indicate onset of *critical phase* and typically occur before defervescence and the onset of shock. The platelet count should be monitored at least every 24 hours initially.
- The white blood cell count can be normal or show leukocytosis during initial phase. Leukopenia, often with lymphopenia, precedes thrombocytopenia and is observed near the end of the febrile phase of illness.

Biochemical Profile

Prothrombin time is prolonged. Activated partial thromboplastin time is prolonged. Low fibrinogen and elevated fibrin degradation product levels are signs of DIC. Hyponatremia is the most common electrolyte abnormality in critical phase. Metabolic acidosis and elevated blood urea is observed in those with shock. Serum glutamic pyruvic transaminase (SGPT) levels elevated. Low serum albumin levels are a sign of hemoconcentration.

Serodiagnosis

Serum specimens should be sent to the laboratory for serodiagnosis, polymerase chain reaction (PCR), and viral isolation. Because the signs and symptoms of dengue fever are nonspecific, attempting laboratory confirmation of dengue infection is important. Serodiagnosis is based on (1) detection of viral nonstructural protein 1 (NS1) during initial illness; (2) detection of IgM antibodies to dengue; or (3) fourfold rise in dengue IgG in paired samples. **Table 1** outlines the desired timing of these tests for confirming the diagnosis. Laboratory criteria for definitive diagnosis include one or more of the following:

1. Isolation of the dengue virus from serum, plasma, leukocytes, or autopsy samples

Table 1 Diagnostic tests for dengue fever

Diagnostic method	Timing of test (after disease onset)	Validity
Virus isolation (culture)	1–5 days	++++
Genome detection (PCR)	1–5 days	++++
Antigen detection (NS1)	1–5 days	+++
Antibody detection (IgM) after 5 days*		++
IgG (paired sera)**	Acute sera 1–5 days; convalescent sera after 15 days	+

*IgM positivity rates: by 3–5 days (50%), 5–7 days (80%), 10 days (90%). IgM appears between 3 days and 10 days and disappears by 2–3 months.

**IgG appears after 1–2 weeks and may persist for life.

2. Demonstration of a fourfold or greater change in reciprocal IgG or IgM antibody titers to one or more dengue virus antigens in paired serum samples. IgM antibody appears early in disease course, requires single sample and is less cross-reactive to other flaviviruses. Thus, measurement of an IgM appears to be most prudent. As per the National Vector Borne Disease Control Programme (NVBDCP), the laboratory test being followed is the IgM antibody-capture enzyme-linked immunosorbent assay (MAC-ELISA) for dengue virus
3. Demonstration of dengue virus antigen in autopsy tissue via immunohistochemistry or immunofluorescence or in serum samples via enzyme immunoassay
4. Detection of viral genomic sequences in autopsy tissue, serum, or cerebral spinal fluid (CSF) samples via PCR.

MANAGEMENT

The mainstay of treatment is supportive therapy. Increased oral fluid intake is recommended to prevent dehydration. Supplementation with IV fluids may be necessary to prevent dehydration and significant hemoconcentration. Fever is managed with paracetamol. Aspirin and nonsteroidal anti-inflammatory drugs should be avoided as these drugs may worsen the bleeding tendency associated with some of these infections. Shock is managed with isotonic fluids. Packed cell transfusion is indicated in refractory shock or if there is significant bleeding.

Patients with known or suspected dengue fever should have their platelet count and Hct measured daily from the third day of illness until 1–2 days after defervescence. Patients with a rising Hct level or falling platelet count should be monitored more frequently. Management of dengue illness can be discussed in three steps:

Step 1: Overall assessment

Step 2: Diagnosis and severity assessment

Step 3: Categorizing into group A, group B, or group C, and treating accordingly.

Overall Assessment

History and Examination

Emphasis in history should be on assessment of *warning signs*. Physical examination should concentrate on hemodynamic assessment, so as to determine the presence and extent of shock, confirming or detecting the warning signs; and checking for bleeding manifestations, abdominal tenderness, mental state and hydration. Tourniquet test is a must.

Investigations

Initial investigations should include an Hct, WBC count, platelet count, and tests to confirm the diagnosis, as described in the section on laboratory diagnosis. In critical phase, additional tests need to be done and include liver function test, renal function test, chest X-ray, serum electrolytes, and ultrasound abdomen.

Diagnosis and Severity Assessment

Determine the phase of disease (febrile, critical, recovery) and severity (nonsevere, severe) of dengue, as per criteria outlined earlier. The child will need admission if any of the following criteria is fulfilled:

1. Presence of any of warning signs
2. Signs and symptoms of hypotension
3. Bleeding from any site
4. Renal, hepatic, or central nervous system (CNS) involvement
5. Pleural effusion or ascites
6. Rising Hct
7. Platelet count less than 50,000/ mm^3 .

Categorize Patients in Group A, B, or C (Table 2)

This step is aimed to place the patient in an appropriate Group (A, B, or C) to decide on future course of action, as follows:

Group A: Patients, who may be sent home

Group B: Patients needing hospitalization

Group C: Patients requiring emergency treatment.

Group A: Home Management

All children who are tolerating oral fluids, passing urine at least once in 6 hours, and not having any of the warning signs can be sent home. Following management needs to be advised:

- Encourage fluid intake; can give oral rehydration salt (ORS), fruit juice, etc. The parents should be advised to increase the amount of oral fluids to be given (e.g., 3–10 kg: 100 mL/kg and 10–20 kg: 75 mL/kg)
- Paracetamol (15 mg/kg/dose) if the child is uncomfortable because of fever. Avoid aspirin, ibuprofen, mefenamic acid, and nimesulide
- Monitor at home for fluid intake, urine output, fever, obvious bleeding, and altered sensorium
- Bring back if any of the above is present or the child develops any of the warning signs.

Group B: Hospital Management

Any patient who fulfills the admission criteria should be admitted (as mentioned above). They may or may not have warning signs. A baseline Hct is measured and monitoring is started. In cases where no warning signs are present, patients should be started on maintenance fluids with isotonic fluid. If patient shows signs of mild dehydration, a correction of 50 mL/kg (< 12 months) and 30 mL/kg (> 12 months) is added to main fluid. At all times clinical parameters are closely monitored and correlated with Hct to guide further fluid therapy. For those who present with warning signs, the following is advised:

Table 2 Treatment of dengue

Category	Patient characteristics	Treatment
A	Accepting orally, passing urine adequately and no warning signs*	<i>Home therapy</i> <ul style="list-style-type: none"> • Increased oral fluids, paracetamol
B	Warning signs* present	<i>Hospitalize</i> <ul style="list-style-type: none"> • Monitor hematocrit, platelets, vitals • Intravenous fluids: titrated as per hematocrit • If worsens, manage as category C
C	Severe bleeding Severe shock Severe organ dysfunction: hepatic, CNS, heart, kidney	<i>Intensive care</i> <ul style="list-style-type: none"> • Monitor hematocrit, platelets, vitals • Treatment of shock: normal saline bolus • Blood transfusion for severe bleeding or clinical worsening. Judicious use of platelets • Supportive treatment for organ failure • Watch for signs of fluid overload, and treat, if detected (oxygen 2, frusemide)

*Warning signs: Abdominal pain, persistent vomiting, mucosal bleed, hepatomegaly, clinical fluid accumulation, lethargy, hemoconcentration, thrombocytopenia

- Start isotonic IV fluids (normal saline or Ringer's lactate) at 5–7 mL/kg/hour for 1–2 hours, reduce to 3–5 mL/kg/hour for 2–4 hours, and then continue with 2–3 mL/kg/hour, according to the response
- Reassess Hct and clinical status
 - If same, continue with 2–3 mL/kg/h for another 2–4 hours
 - If clinical status worsens or Hct rises, increase rate of fluids to 5–10 mL/kg/hours for 1–2 hours
- Reassess clinical status, repeat Hct and review fluid infusion rates, till the child is better
 - If the child improves, maintain minimum IV fluids at 0.5 mL/kg/hour for 24–48 hours. Stop fluids when child demands and accepts adequate oral fluids, and food
 - Those who worsen or develop profound shock, bleeding or multisystem involvement, manage as for Group C.

Group C: Emergency Treatment

Emergency treatment is required in children with severe dengue or those in critical phase, as follows:

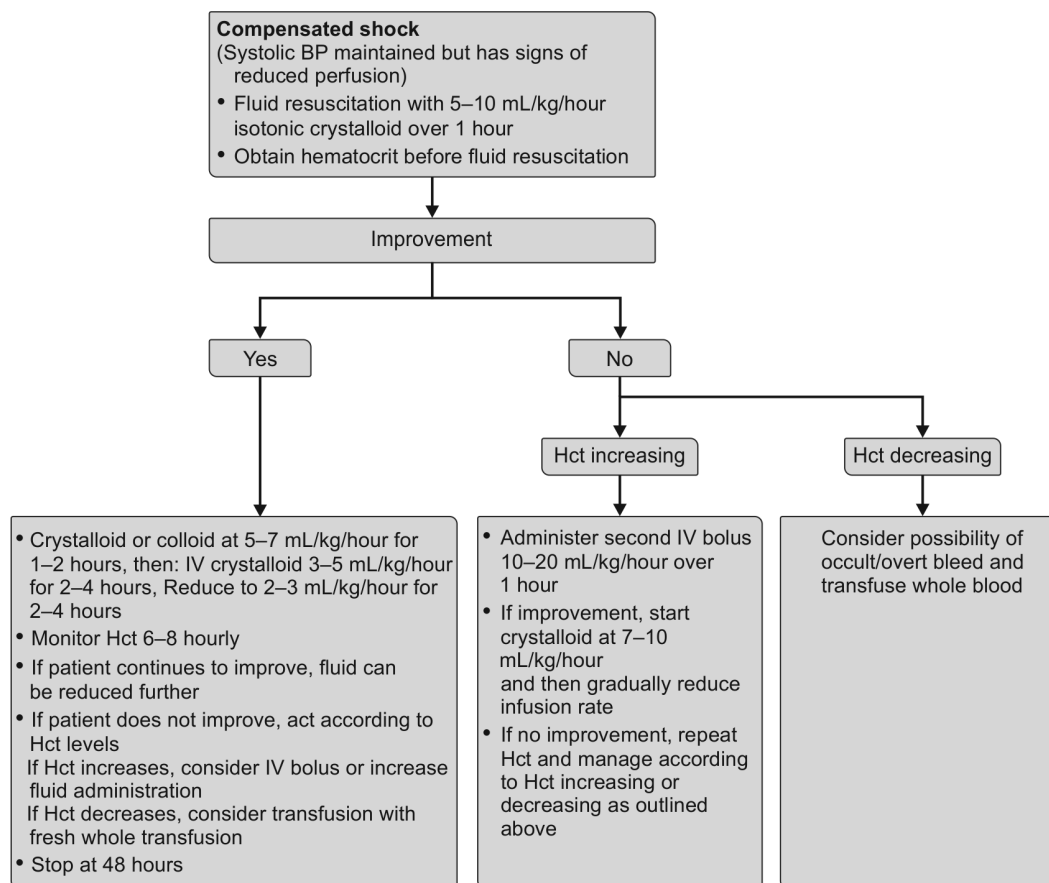
- Obtain Hct, blood count, and other organ function tests, as indicated.
- *Compensated shock:* In these children, fluid resuscitation is started at 5–10 mL/kg/hour, and further directed as per **Flow chart 1**.
- *Hypotensive shock:* Administer isotonic fluid bolus 20 mL/kg in 15 min. For further management, follow the algorithm depicted in **Flow chart 2**.
- *Hemorrhagic complications:* Suspect severe bleeding if there is an unexplained fall in Hct, refractory shock not responding to 40–60 mL/kg of fluid, and persistent or worsening metabolic acidosis. Packed cell transfusion 10 mL/kg over 2–3 hours can be lifesaving in these children. There is not much evidence for platelet transfusion or fresh frozen plasma for severe bleeding. Platelet transfusions should not be used prophylactically. Its use has neither shown to prevent progression to severe bleeding nor does it shorten the bleeding time and may instead be associated with severe side effects. Platelet transfusion should be restricted to cases with severe bleeding only.
- *Monitoring:* This essentially remains the basic prerequisite for treating children with severe dengue, in an emergency setting.
 - Monitor vital signs and peripheral perfusion 1–4 hourly unless patient is out of critical phase. Monitor Hct before and after fluid replacement, then 6–12 hourly.
 - Monitor blood glucose and other organ dysfunction both clinically and biochemically.
 - A typical monitoring chart for dengue fever should record the following: body temperature, heart rate, blood pressure, pulse volume, capillary refill time, abdominal pain, appetite, abdominal pain, vomiting, bleeding and sensorium.

Treatment of Fluid Overload

A patient with dengue can have fluid overload due to excessive or rapidly transfused IV fluids, use of hypotonic fluids, and inappropriate use of fresh frozen plasma or platelets. Another important reason is continuation of IV fluids even during the phase of plasma reabsorption and recovering.

These children may present with features of pulmonary edema or congestive heart failure. Following management is suggested:

- **Oxygen Management of Other Complications**
Encephalopathy in dengue may result due to intracranial bleeding, electrolyte disturbances, occlusion due to DIC or hepatic encephalopathy. Appropriate diagnosis for cause and specific

Flow chart 1 Algorithm for fluid management in compensated shock

management should be instituted. Cardiac involvement may be seen during shock or during convalescence, which may manifest as arrhythmias or heart failure.

Criteria for Discharge

Patient should be discharged only if he has been afebrile for at least 24 hours, passing urine normally, having improved appetite and has no respiratory distress. His laboratory parameters should show a stable Hct and platelet count of more than 50,000/mm³.

PREVENTION AND CONTROL

Aedes aegypti should be the main target of surveillance and control. The NVBDCP was launched in 2003 which extended vector control services for dengue and Japanese encephalitis. A mid-term plan was approved in 2011 to enhance the country's capacity to control dengue. The activities targeted against dengue include:

- Increasing diagnostic facilities. Introduction of ELISA-based NS1 antigen for diagnosis of dengue early in disease
- Monitoring and surveillance of vector control
- Capacity building of medical health personnel
- Increasing social mobilization through information, education and communication (IEC) activities for vector control.

Surveillance

Disease Surveillance

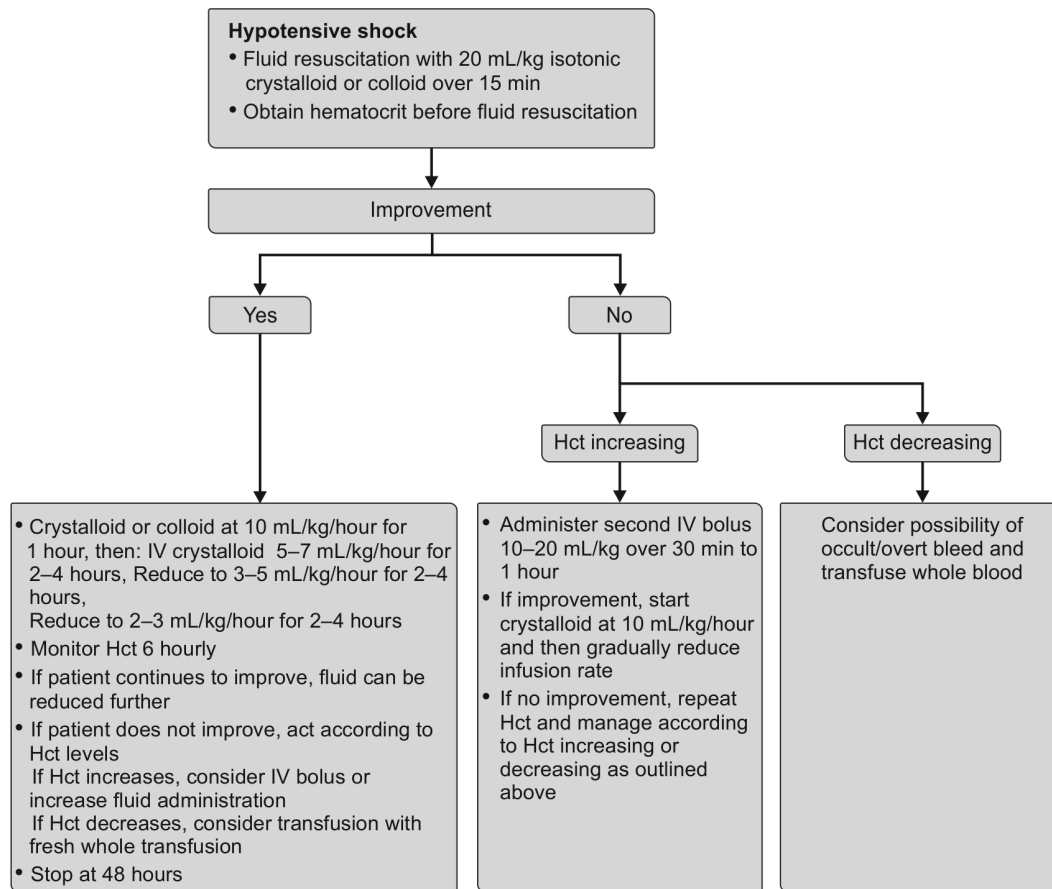
Tracking the number of suspected and confirmed infected human cases. It also includes recording the circulating serotypes of dengue and the number of deaths from dengue.

Vector Surveillance

Tracking mosquito populations in areas of potential risk. Mainly two indices are used for measuring the vector density. These are (1) *house index*; and (2) *Breteau index*. House index is defined as the percentage of houses positive for the larvae; and Breteau index as the number of containers positive for the larvae per 100 houses. These indices measure larval infestation rather than adult mosquito density. Epidemic spread of *Aedes* has been reported with *house index* as low as 1% in Indian settings.

Monitoring Behavioral Impact

Communication for behavioral impact (COMBI) is a methodological process where communication interventions are used to help a community adopt healthy behaviors aimed to reduce mosquito multiplication and spread. The surveillance is done by observing whether such behaviors are adopted and sustained by the community.

Flow chart 2 Algorithm for fluid management in hypotensive decompensated shock

Long-term Vector Control

Adequate water supply is a must. Sprays of larvicides are recommended in high-risk localities. All objects that may collect water (old tyres, broken jars, empty tins and bottles) should be disposed off. Water should be changed routinely in water coolers, flower vases, and overhead tanks. Coolers, if not in use should be drained and mopped dry. Large tanks with taps should be kept covered. Management of roof tops, porticos and sunshades to be encouraged. Health education should be provided regularly in schools and through mass media. Sensitize and involve the community for detection of *Aedes* breeding places and their elimination.

Biological and Chemical Control

Use of larvivoracious fish in ornamental tanks, fountains, or biocides can kill the larval stages. Use chemical larvicides like *Abate*® in big breeding containers. Aerosol space spray during daytime may be another option in high-density areas. There has been recent research exploring the control of *Aedes* mosquito by genetically engineering male insects which carry dominant lethal gene (RIDL) at both pupa and adult stages.

In recent years, interest in mosquito-killing (entomopathogenic) fungi is reviving, mainly due to continuous and increasing levels of insecticide resistance and increasing global risk of mosquito-borne diseases. Particular focus is on species belonging to the genera *Lagenidium*, *Coelomomyces*, *Entomophthora*, *Culicimycetes*, *Beauveria*, and *Metarhizium*.

Vaccine Development

Development of a multivalent vaccine against all four serotypes seems necessary. Progress in vaccine development is slow because these viruses grow poorly in cell culture and there is no acceptable animal model for dengue illness.

A live attenuated tetravalent dengue vaccine (CYD-TDV) has been developed which contains four dengue virus with expression of dengue premembrane and envelope protein and nonstructural and capsid protein of yellow fever strain (YF-17D). The vaccine is administered as three dose schedule and has shown good protection against dengue serotype 1, 3 and 4. The vaccine is still under multicentric phase III trials. Several research groups are successfully exploring an infectious clone technology for the development of a dengue vaccine. The Chimeri Vax™ system, originally developed to construct JE vaccine, has now been applied to dengue viruses. This vaccine was shown to be safe and immunogenic in a monkey study. Another approach is based on the use of a dengue type 4 mutant containing a deletion for the construction of a dengue chimeric vaccine. Phase I clinical trials of a deletion mutant carried out in adult humans showed good safety and immunogenicity.

In India, the yeast, *Pichia pastoris* has been used to develop a noninfectious dengue virus like particle consisting of viral envelope protein using recombinant DNA technology. The vaccine is under trial.

IN A NUTSHELL

1. Dengue is spread by *Aedes* mosquito which multiplies in collections of stagnated water.
2. Four different serotypes of virus exist. Antibody against one serotype does not confer protection against another. Rather, the illness is more severe following secondary infection in a child sensitized against a different serotype earlier.
3. Increased capillary permeability and coagulopathy chiefly contribute to disease manifestations. Thrombocytopenia occurs both due to bone marrow suppression and immune-mediated destruction.
4. Clinical presentation consists of a biphasic fever, myalgia, arthralgia, and hemorrhagic manifestations, lasting over 3–7 days. The most vulnerable stage is soon after defervescence (critical phase) characterized by increased capillary permeability.
5. Serological diagnosis is possible by detecting nonstructural (NS) antigen 1 between 2 days and 5 days, detection of IgM antibodies between 5 days and 10 days, or fourfold rise in IgG antibodies after 7–10 days.
6. Children with *warning signs* should be hospitalized. Those with severe shock, severe bleeding and organ involvement need management in intensive care unit (ICU) setting.
7. Fluid therapy is the mainstay of treatment. Crystalloid is the fluid of choice during resuscitation. Best guide to fluid therapy is Hct.

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Chapter 31.17

Chikungunya Fever

Rajniti Prasad

Chikungunya, a viral fever, is caused by an alphavirus [chikungunya virus (CHIKV)] and spread by bite of an infected *Aedes aegypti* mosquito. The disease was first described in 1955 following an outbreak on the Makonde plateau. The name derives from kungunyala, meaning *to dry up or become contorted*. Although primarily African and zoonotic disease, non-African large urban outbreaks have been reported, which is transmitted by the same vectors as those of dengue viruses. Since then, CHIKV has caused numerous outbreaks and epidemics in both Africa and Southeast Asia, affecting many children.

CHIKUNGUNYA VIRUS

Chikungunya virus, a positive strand, enveloped RNA virus, is a member of the alphavirus of *Togaviridae* family. It is closely related to o'nyong-nyong viruses. Three distinct phylogroups were reported on the basis of E1 envelope glycoprotein gene sequence: first contained all isolates from West Africa, second comprised all Central, Southern and Eastern African (CSEA) strains and third isolates from Asia. Complete genomic sequence of CHIKV has 11,805 nucleotides in length. Coding sequences consist of two large nucleotides, encoding the nonstructural polyprotein and structural polyprotein. The nonstructural polyprotein is the precursor of proteins nsP1, nsP2, nsP3 and nsP4 and structural polyprotein is the precursor of protein C, E2, E3, 6K and E1.

EPIDEMIOLOGY

The outbreak of CHIKV is being reported from different parts of India. The current outbreak in India started in late 2005, when cases of suspected fever were reported from coastal parts of Andhra Pradesh and Karnataka. The confirmed cases of chikungunya fever have been reported from all over India but more so from Andhra Pradesh, Karnataka, Maharashtra, Tamil Nadu, Madhya Pradesh and Gujarat states. The attack rate varies from 8% to 45%.

VECTOR

Aedes aegypti, *A. albopictus* and *A. polynesiensis* are commonly involved in the transmission of virus, although *Culex* has also been reported for the transmission. *A. aegypti* is the principal vector of CHIKV in India. This vector is anthropophilic, endophagic and bites during the daytime. It mainly breeds in man-made containers such as coolers, cisterns, wells, water-storage containers, etc. Both *A. aegypti* and *A. albopictus* are present in the United States of America and Europe, thus virus could expand to new geographic locations.

TRANSMISSION

Chikungunya virus is commonly transmitted to humans through the bite of infected *Aedes* mosquitoes. Vertical transmission, occupational exposure and occurrence in a health worker from careless handling of patient's blood have also been reported. In Africa, monkeys and other wild primates may also serve as reservoirs of the virus.

PATHOGENESIS

Chikungunya virus replicates in fibroblasts, monocytes, macrophages, natural killer cells, epithelial and endothelial cells.

T and B lymphocytes and monocyte-derived dendritic cells are not susceptible. Viral entry occurs through a pH-dependent, endocytic pathway. CHIKV is highly cytopathic for mammalian cells, and causes apoptosis of infected cells. The replication of virus is inhibited by interferon. In humans, CHIKV produces clinical manifestations about 48 hours after mosquito bite. Patients have high viremia during the first 2 days, declines around day 3 or 4 and usually disappear by day 5. Hemagglutination inhibition and neutralizing antibodies can be detected after day 5 with declining viremia. Silent CHIKV infections do occur. A single infection; clinical or silent confers lifelong immunity. The enhanced expression (upregulation) of cytokines such as interleukin (IL)-1 and IL-6 is associated with severe CHIKV-induced disease.

CLINICAL MANIFESTATIONS

Chikungunya is an acute infection characterized by acute onset of high fever, severe arthralgia, myalgia and skin rash lasting for a period of 1–7 days (triad: fever, rashes and arthralgia). The incubation period is usually 2–4 days, with a range of 1–12 days. All age groups are affected. Fever rises abruptly, often reaching 39–40°C accompanied by chills, myalgia, headache and photophobia. This acute phase lasts 2–3 days. The temperature may remit for 1–2 days, after a gap of 4–10 days (saddleback fever).

The arthralgia is polyarticular, migratory and predominantly affects the small joints of hands, wrists, ankles, elbows and feet with lesser involvement of larger joints. In acute stage, children complain severe pain on movement and bending forward (**Fig. 1**). Pain is worse in the morning, improved by mild exercise and exacerbated by strenuous exercise. Swelling may occur but fluid accumulation is uncommon. About 12% of serologically positive cases have been reported to have residual joint symptoms such as joint stiffness, swelling and pain 3 years after initial infection.

Cutaneous manifestations include flushing of the face and trunk. This is usually followed by maculopapular rash and occasionally petechiae. Trunks and limbs are commonly involved,

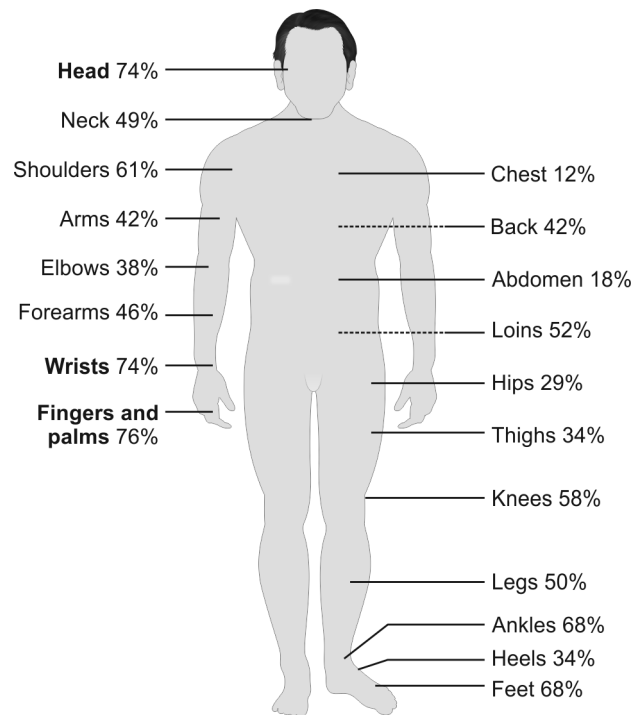


Figure 1 Frequency of pain by location during acute stage of chikungunya infection

but face, palms and soles may also show lesions. Rashes may simply fade or desquamate. Exacerbation of existing dermatoses such as psoriasis, and Hansen's disease have been observed.

Iridocyclitis and retinitis are the most common ocular manifestations and have benign clinical course. Less frequent ocular lesions include episcleritis. Diarrhea, vomiting and abdominal pain have been reported in about 50% of patients. Neurological manifestations include acute encephalopathy, encephalitis, febrile seizure, acute flaccid paralysis and Guillain-Barré syndrome. Other manifestations include congestive cardiac failure, pneumonia, fulminant hepatitis, acute kidney injury and respiratory failure. Hemorrhagic manifestations are rare, but are an important distinguishing feature from dengue fever.

The majority of children develop chronic stage of the disease, which is characterized by pains in joints and/or bones or both exacerbation and remission. The case fatality rate is about 1 in 1,000 during epidemics. The common causes of death are heart failure, multiple organ failure, hepatitis and encephalitis.

DIAGNOSIS

The diagnosis of chikungunya is based on clinical, epidemiological and laboratory findings. However, an acute onset of fever and severe arthralgia or arthritis in children unexplained by other medical disorder should be considered as possible case of chikungunya. Laboratory investigation is essential to establish diagnosis and initiate specific public health response. Three main laboratory tests used for diagnosis of chikungunya fever include (1) virus isolation, (2) polymerase chain reaction (PCR) and (3) serological tests.

Virus isolation is the most definitive tests. CHIKV produces cytopathic effects in a variety of cell lines including BHK-21, HeLa and Vero cells. The cytopathic effects must be confirmed by CHIK specific antiserum and results can be available in 1–2 weeks. *Reverse transcriptase PCR* (RT-PCR) technique for diagnosis has been developed using nested primer pairs amplifying specific components of three structural gene regions, capsid (C), envelope E2 and part of envelope E1. RT-PCR can detect viral nucleic acid in blood 1 day before to 7 days after onset of symptoms. PCR results can be available within 1–2 days.

Serologic diagnosis can be made by demonstration of fourfold increase in antibody in acute and convalescent sera or demonstrating immunoglobulin M (IgM) antibodies specific for CHIKV. A commonly used test is IgM antibody-capture enzyme-linked immunosorbent assay (MAC-ELISA). Results of MAC-ELISA can be available within 2–3 days. Cross-reaction with other flavivirus antibodies such as O'nyong-nyong and Semliki may occur; however, the latter viruses are relatively rare in Southeast Asia. Further confirmation can be done by neutralization tests and hemagglutination inhibition assay (HIA). A positive virus culture supplemented with neutralization is taken as definitive proof for the presence of CHIKV. The diagnostic criteria of chikungunya fever are summarized in **Table 1**.

MANAGEMENT

There is no specific treatment for chikungunya fever. The illness is usually self-limiting and resolves with time. Supportive care with rest is recommended during the acute stage. Movement and mild exercise tend to improve stiffness and morning arthralgia, but heavy exercise may exacerbate symptoms. Nonsteroidal anti-inflammatory drugs (NSAIDs) are recommended. In unresolved arthritis refractory to NSAID, chloroquine (10 mg/kg/day) has proved to be useful. Chloroquine inhibits viral replication by

Table 1 Diagnostic criteria of chikungunya fever

Criteria	Definition
<i>Clinical</i>	<i>Possible case:</i> When not explained by other medical condition: dengue or alphavirus infection, arthritic disease, endemic malaria
• Acute onset of fever > 38.5°C and severe arthralgia or arthritis	
<i>Epidemiological</i>	<i>Probable case:</i> If clinical and epidemiological criteria are met: other pathogens with similar clinical manifestations can cocirculate within the same geographical regions
• Residing in or visited epidemic area within 15 days before onset of symptoms	
<i>Laboratory</i>	<i>Confirmed case:</i> If a patient tests positive for one of the laboratory, irrespective of clinical manifestations
• Virus isolation	
• Presence of viral RNA	
• Specific IgM antibodies	
• Fourfold increase in IgG titers in paired samples	

blocking the pH-dependent endocytosis of CHIKV into host cells. Although chloroquine blocks CHIKV replication, the therapeutic (antiviral) index of chloroquine in cell cultures is narrow thus, one should be cautious when planning the use of chloroquine. Ribavirin has some antiviral activity and showed moderate beneficial effect in alleviating arthralgia and swelling. Although ribavirin has some antiviral properties against CHIKV, interferon- α is more effective in inhibiting CHIKV replication.

Self-resolution occurs with cutaneous lesions. Patients with hyperpigmentation may be treated with sunscreens and topical steroids and improve over 3 weeks. Patients with more diffuse involvement showed a slower resolution. Aphthous ulcers usually heal over 7–10 days with local cleaning and topical antimicrobials. Iridocyclitis and retinitis usually have a benign clinical course and do not require any treatment. Vision is usually preserved.

Infected persons should be protected from further mosquito exposure (staying indoors and/or under mosquito net during the first few days of illness) so that they cannot contribute to the transmission cycle.

PREVENTION AND CONTROL

Prevention is mainly aimed to avoid mosquito bites and elimination of mosquito breeding sites including use of full sleeve clothes and long dresses to cover the limbs, mosquito coils, repellents and electric vapor mats during the daytime. Use of permethrin-treated mosquito nets to protect babies, old people and others who may rest during the day. Drainage of water from coolers, tanks, barrels, drums and buckets when not in use is advocated.

Vaccine

The widespread geographic distribution, recurrent epidemics and infection of military personnel, travelers, and laboratory staff working with CHIKV have indicated the need for a safe and efficacious vaccine. In Thailand, CHIK strain 15561 was used to develop a small lot of vaccine. The vaccine produced no untoward reactions and was highly immunogenic. The current live vaccine (Lot 1-85, TSI-GSD-218) was developed in the United States in the US Army Medical Research Institute of Infectious Diseases (USAMRIID) and was produced at the Salk Institute, from GMK strain 15561 by serial passage in MRC-5 cells. The results of phase I and phase II trials strongly suggest that the live vaccine is safe and well-tolerated and produces no severe or frequent symptoms.

IN A NUTSHELL

1. Chikungunya is caused by an alphavirus (CHIKV) and spread by bite of an infected *A. aegypti*.
2. The classical triad consists of fever (saddleback type), maculopapular rashes and arthralgia.
3. Arthralgia is polyarticular, migratory and predominantly affects the small joints of hands, wrists, ankles, elbows and feet.
4. The diagnosis is based on clinical, epidemiological and laboratory findings, which include virus isolation, PCR and serological tests.
5. It is a self-limiting disease and resolves with time. Supportive care with rest is recommended during the acute stage. NSAIDs are recommended. In unresolved arthritis refractory to NSAID, chloroquine (10 mg/kg/day) has proved to be useful.

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Chapter 31.18

Viral Hemorrhagic Fevers

Nigam Prakash Narain, Priya Verma

Viral hemorrhagic fevers (VHFs) refer to diseases caused by distinct families of enveloped RNA viruses. The disease process encompasses a multisystem involvement with breakdown of the entire vascular machinery of the body and the mechanisms that regulate the body's internal homeostasis; with widespread hemorrhage that represents these infections. Some of these viruses cause relatively mild illnesses, but in most cases the disease is fatal. VHF viruses are enveloped viruses with single-stranded RNA genomes and vary greatly in their morphology. They are members of four distinct families: (1) *Arenaviridae*—Lassa, Junin, Machupo, Sabia and Guanarito viruses; (2) *Bunyaviridae*—Rift valley fever (RVF), Crimean-Congo hemorrhagic fever (CCHF) and agents of hemorrhagic fever with renal syndrome; (3) *Filoviridae*—Ebola and Marburg viruses; and (4) *Flaviviridae*—yellow fever, Kyasanur forest virus, dengue, Omsk and Alkhurma viruses. Some of the hemorrhagic fever viruses viz. Ebola, Marburg, Lassa fever and the New World arenaviruses have a propensity to cause infection through aerosol dissemination that makes them formidable candidates as weapons for biological warfare. In this chapter, we shall focus only on these VHF viruses. Dengue fever is already discussed.

EPIDEMIOLOGY

The VHF viruses are associated with sporadic disease and epidemics. The natural reservoir of these viruses is a nonhuman vertebrate or an arthropod. Humans are incidental hosts.

Arenaviridae

The viruses causing hemorrhagic fevers are broadly distributed over two continents. Lassa virus is endemic to the region of West Africa while the viruses endemic to the South American continent viz. Junin, Machupo, Guanarito and Sabia viruses are collectively referred to as the Latin American hemorrhagic fever viruses.

Bunyaviridae

Rift valley fever is endemic to sub-Saharan Africa. It caused large epidemics in Kenya and Somalia in 1997–1998, Tanzania 2006–2007 and in the South African nations of Botswana and Namibia in 2010.

Filoviridae

Marburg virus was first isolated in 1967 from cases of hemorrhagic fever in European laboratory workers working with tissues from African green monkeys imported from Uganda. Ebola virus was first reported in Zaire and Sudan and was associated with high case fatality rates. Subsequently a third subtype Ebola (Reston) and a fourth subtype were found in an animal worker in Côte d'Ivoire. Fruit bats are the natural reservoirs for filoviruses. The Marburg virus and subtypes of Ebola Sudan, Zaire and Côte d'Ivoire are restricted geographically to the African continent.

Flaviviridae

Kyasanur forest virus was discovered in a sick monkey in the Kyasanur forest in India in 1957. Annual cases reported are approximately 400–500. The yellow fever virus is endemic to the sub-Saharan African regions. Annual incidence is estimated to be 200,000 cases globally. Dengue virus is prevalent throughout Asia and Africa.

TRANSMISSION

The routes of transmission of the VHF viruses are variable but most are zoonotic with spread via arthropod bites or contact with infected animals. The viruses are carried in rodents and transmitted through the urine, saliva and other body excretions from infected rodents. Zoonotic spread may occur through:

- Livestock via consumption of raw meat from potentially infected animals and unpasteurized milk (RVF virus)
- Rodents via inhalation of aerosols or contact with rodent excreta (arenavirus, hantavirus)
- Other reservoir species such as bats (Ebola and Marburg viruses).

Vector-borne transmission also occurs via mosquitoes, *Aedes* (RVF virus, yellow fever) or tick bites or crushing of infected ticks [CCHF, Kyasanur forest disease (KFD)]. Person-to-person spread is another important mode of transmission for many of the viruses especially the filoviruses through contact with infected blood and body secretions. Nosocomial transmission may also occur through the reuse of needles, syringes and exposure to infected body fluids and hospital waste as a fallout of nonadherence to infection control measures in a hospital setting.

PATHOGENESIS

The viral agents causing severe hemorrhagic fevers are all single-stranded RNA viruses that can infect man either through contact with animal reservoirs or arthropod vectors. Increased risk for exposure is seen with travel to countries where VHFs are endemic. Those involved with animals (slaughter houses, animal research) and health-care workers are also at risk. There is no racial and sex predilection, but young children have the greatest susceptibility. In the later stages of the illness, the viral loads are quite high. This period carries the highest risk for disease transmission.

There is dysregulation of the innate immune response, although replication of the viruses in target cells and tissues can directly contribute to the pathological manifestations of VHF. Factors that may contribute to this subversion of the host immune response include the rapid infection and impairment of dendritic cells leading to a sudden and enigmatic death of lymphocytes. The virus-infected cells then liberate a variety of inflammatory mediators. These cause an irreversible alteration in the vascular function and integrity and trigger widespread dysfunction of the coagulation mechanisms which is the hallmark of the VHFs.

PATHOLOGY

Widespread necrosis is seen in many organ systems, together with serous effusions and hemorrhages that are so characteristic of these diseases. The liver is extensively involved to extent of massive hepatocellular necrosis and failure. Diffuse alveolar hemorrhage and interstitial pneumonitis occurs in the lungs. The kidney shows features of acute tubular necrosis and microvascular thrombosis.

CLINICAL FEATURES

The illness is characterized by sudden onset of high-grade fevers with myalgia and severe prostration. Bleeding manifestations become evident in the form of petechial hemorrhages in the skin, ecchymoses or a more severe generalized bleeding.

Arenaviruses

The incubation period is 10–14 days. There is a gradual onset of fever with cough and pharyngitis. Vomiting is common. Later, bleeding manifestations and neurological features such as convulsions and coma occur. In newborns, Lassa fever leads to anasarca and shock.

Bunyaviruses

Flu-like symptoms occur but patients recover without complications. The incubation period is 2–6 days. The illness begins with fever, nausea, vomiting and abdominal pain. Hemorrhagic disease occurs in less than 20% cases. Ocular involvement can manifest as retro-orbital pain, retinitis and visual loss. Neurological dysfunction and renal failure occur in the later stages of the illness.

Filoviruses

The incubation period for both Marburg and Ebola viruses is 2–21 days. The disease begins with an acute onset of high-grade fever with headache, myalgia and arthralgia. These symptoms last less than a week. This is followed by a maculopapular rash and hemorrhage. Hepatitis and pancreatitis are quite common. Shock and disseminated intravascular coagulation (DIC) with multiorgan failure occur in severe cases after the second week of illness.

Flaviviruses

The incubation period in the human host is 3–6 days. After the initial viral prodrome, the illness can either resolve spontaneously or undergo remission for a short period and evolve into a fulminant infection. Bleeding diathesis with shock and myocardial dysfunction can occur. Yellow fever virus is hepatotropic and can lead to hepatocellular failure.

DIFFERENTIAL DIAGNOSIS

In the absence of a specific diagnostic test, a high index of clinical suspicion is required to diagnose VHF. They are often difficult to diagnose in the initial few days of the illness because they present with nonspecific viral prodromal features.

Infections that need to be differentiated from a VHF include malaria, meningococcal bacteremia, gram-negative bacteremia, rickettsial infections, influenza, leptospirosis, salmonellosis, Q fever, toxic shock syndrome, hemorrhagic varicella, hemorrhagic measles and septicemic plague. Noninfectious differentials include thrombotic/immune thrombocytopenic purpura, acute leukemia, hemolytic uremic syndrome and various collagen vascular diseases.

DIAGNOSIS

Viral hemorrhagic fever should be considered in any patient with the following clinical presentation in the absence of an alternative diagnosis:

- Acute fever of duration less than 3 weeks in a severely ill patient
- Hemorrhagic manifestations (at least two of the following: petechial rash, epistaxis, hematemesis, hematochezia/malena or any other bleeding)
- No predisposing factors for a bleeding diathesis.

Laboratory findings are nonspecific and include leukopenia (except in Lassa fever), thrombocytopenia, elevated transaminases, increased serum bilirubin, anemia or hemoconcentration, prolonged prothrombin time (PT), activated partial thromboplastin time (APTT) and bleeding time, elevated fibrin degradation products (FDPs), hypofibrinogenemia, proteinuria, hematuria and increased blood urea nitrogen (BUN) and serum creatinine.

Immunological evidence of infection can be obtained by antigen capture testing by enzyme-linked immunosorbent assay (ELISA), and antibody testing in paired sera. Combined antigen and antibody testing has high specificity and sensitivity for early diagnosis of Lassa fever and the results have prognostic value (presence of indirect fluorescent antibody early in disease is associated with high mortality).

Viral isolation in cell culture is currently the gold standard of viral detection; however, this may only be undertaken at a research and biosafety level 4 (BSL-4) facility. Virus can also be detected by polymerase chain reaction (PCR). Clinical specimens in an outbreak

need to be sent to the Centers for Disease Control and Prevention (CDC) or the US Army Medical Research Institute of Infectious Diseases (USAMRIID). Postmortem skin biopsies fixed in formalin and blood collected within a few hours of death by cardiac puncture can be used for diagnosis. Samples should be sent for testing to a reference laboratory with BSL-3 and BSL-4 capability.

MANAGEMENT

The medical management should follow the guidelines in **Table 1**.

Supportive Care

Supportive care includes maintenance of fluid and electrolyte balance and circulatory volume. Mechanical ventilation, dialysis and appropriate therapy for secondary infections may be indicated. Anticoagulant therapy, aspirin, nonsteroidal anti-inflammatory medications and intramuscular injections are contraindicated.

Ribavirin Therapy

Ribavirin is recommended for (1) those with VHF of unknown etiology pending viral identification; and (2) suspect, probable or confirmed cases caused by an arenavirus or bunyavirus. Ribavirin is not recommended for filoviruses and flaviviruses.

PROGNOSIS

Mortality for arenavirus infections ranges from 5% to 35%. Up to one-third of Lassa fever survivors develop sensorineural deafness. Case fatality rate in humans is 1% for RVF and 1–50% for the hantaviruses. Case fatality rate for Marburg hemorrhagic fever ranges from 23% to 70% and 50–90% for Ebola hemorrhagic fever. Complications and sequelae include arthralgia, parotitis, transverse myelitis and pericarditis. Fetal and neonatal infections are associated with high mortality. Infections with yellow fever are usually mild; however, patients may develop severe illness with fulminant hepatitis, coagulopathy and overt bleeding. Case fatality depends on the epidemic but may reach up to 50% in severe cases.

PREVENTION

The CDC and WHO have developed practical hospital-based guidelines *Infection Control for Viral Hemorrhagic Fevers in the African Health Care Setting*. The manual can help health care facilities recognize cases and prevent hospital-based disease transmission with few financial resources. Health care workers

Table 1 Management of viral hemorrhagic fevers

Categorization	Medical management
A. Exposed persons	Medical surveillance. No postexposure prophylaxis is recommended*
B. Suspected VHF case of unknown viral type	Supportive care + Ribavirin** therapy
C. Suspected or confirmed VHF case known to be caused by an flavivirus or filovirus	Supportive care only
D. Suspected confirmed VHF case known to be caused by an arenavirus or bunyavirus	Supportive care + Ribavirin therapy

*A previous CDC recommendations state that ribavirin should be given to high-risk contacts of persons with Lassa fever. The Working Group on Civilian Biodefense recommends medical surveillance only, and notes that the CDC guidelines may be under review.

**Ribavirin therapy should be initiated promptly unless another diagnosis is confirmed or the etiologic agent is known to be a flavivirus or filovirus.

should use standard contact and droplet precautions with eye protection while attending the VHF patients. Prevention should also focus on avoiding contact with vectors in endemic countries. The only licensed vaccine, at present, is available against yellow fever.

IN A NUTSHELL

1. Viral hemorrhagic fevers are caused by four viruses from different families with clinical severity ranging from mild to potentially serious with multisystem involvement.
2. Diagnosis in the initial 3–7 days of illness is difficult since they mimic influenza-like syndromes.
3. Doctors should immediately notify their laboratories and the concerned local health department when VHF is suspected.
4. Virus can only be detected in laboratories equipped with BSL-3 and BSL-4 precautions.
5. There is no established treatment, therefore preventive strategies form the cornerstone of management.
6. The mainstay of management involves hospitalization and supportive care.
7. Survivors might develop disabling complications like deafness, uveitis and postencephalitic sequelae.
8. Preventive efforts should focus on community-wide vector control.
9. Viral hemorrhagic fever viruses can serve as potential weapons for bioterrorism.

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Chapter 31.19

HIV and Acquired Immunodeficiency Syndrome

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Human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS) caused by HIV-1 and HIV-2 viruses has been one of the most devastating infections faced by mankind for the last three decades. Although initially a disease of the so called *high risk population*, this disease has gradually and eventually penetrated upto all sections of the society. Though children form only about 6% of the global HIV burden, they suffer more due to rapid progression with consequent higher mortality. Due to the availability of treatment and better access to antiretroviral therapy (ART), as well as the availability of drugs to treat opportunistic infections (OIs), the (HIV) disease has now been converted to a chronic disorder with longer survival. The HIV infection (besides being a chronic medical disorder), has many social ramifications (particularly in children, due to demise of parents and broken families) and economic adversities. Though the HIV *epidemic* appears to have currently stabilized, it is still an important disease contributing to significant morbidity and mortality in the developing world.

THE PROBLEM STATEMENT

As per the UNAIDS (United Nations Program on HIV/AIDS) report on global AIDS epidemic, 35.3 million people were living with HIV or AIDS in 2012, of which 3.3 million were children less than 15 years of age. In the year 2012, there were 1.6 million deaths due to AIDS-related causes worldwide (around 30% decline from the mortality in 2005). Following the same trend, childhood AIDS related deaths have also reduced from 320,000 in the year 2005 to 210,000 in the year 2012.

Due to scaled-up and improved HIV prevention services, the annual number of newly infected children in the year 2012 was 260,000 in low- and middle-income countries, 35% lower than that in 2009. From 2001 to 2012, there was a 52% decline in new HIV infections among children. In the year 2012, more than 9.7 million people living with HIV were receiving ART in low- and middle-income countries, of which 630,000 are children under 15 years of age. Over the past few years (2009–2012), improved access to healthcare services to prevent mother-to-child transmission has prevented 670,000 children from acquiring HIV infection.

In the *South and Southeast Asia*, 3.9 million people were living with AIDS in 2012, of which 200,000 were children less than 15 years of age. Every year, around 21,000 children are newly infected with HIV, while 13,000 die due to AIDS related causes in this geographical region. There were 0.116 million new HIV infections in adults and 14,500 new HIV infections amongst children in the year 2011. India observed around 0.148 million deaths in 2011 due to AIDS related causes of which 7% were children. Despite a declining trend in the adult HIV prevalence in the high prevalence states in India, there has been a rising trend in many other states in the North, North-East and North-West.

THE VIRUS

Human immunodeficiency virus is a lymphotropic ribonucleic acid (RNA) retrovirus. It belongs to the genus *Lentivirus* and subgroup *Retrovirus*. There are two types, HIV-1 and HIV-2, of which the type HIV-1 is predominant worldwide and the type 2 is concentrated in

West Africa. HIV is further classified into the *major* M group which contributes to more than 90%, *outlier* O group found in Western and Central Africa and *new* N group which was discovered in 1998. The M group shows nine distinct genetic subtypes A, B, C, D, E, G, H, J and K. Subtype C is predominant subtype in the Indian population.

The HIV-1 virus contains two identical strands of HIV-RNA, enzymes and accessory proteins; surrounded by bullet shaped core/capsid. The HIV-1 genome consists of *long terminal repeats* at either ends (which regulate and express the HIV genes) and three major sections in between the GAG region which encodes viral core proteins (e.g., p24), the POL region which encodes viral enzymes (e.g., reverse transcriptase and protease) and the ENV region which encodes viral envelope proteins (e.g., gp120 and gp41). In addition, it also has accessory and regulatory proteins (nef, vif, vpr, etc.) which aid in viral replication. The external glycoprotein gp120 attaches to the CD4 cell receptors by binding to the coreceptors (CCR5 and CXCR4) on the cell surface.

After binding, gp41 is inserted into the CD4 cell, resulting in membrane fusion and fusion with pores. The viral core is released into the CD4 cell cytoplasm and the HIV genome is reverse transcribed to deoxyribonucleic acid (DNA) by the reverse transcriptase. This step being highly error-prone, it can generate mutations or quasispecies, which enables the virus to escape recognition by cellular immunity system. Viral DNA is transported to the nucleus and inserted into the host DNA by viral integrase. This is referred to as *provirus* having the advantage of latency or dormancy for long periods. The translated viral proteins are processed subsequently by viral proteases and assembled into new virions, which on release from the cell, infect other target organs and complete the viral life cycle.

PATHOGENESIS

Human immunodeficiency virus is lymphotropic and selectively binds to CD4 expressing cells, i.e., helper T lymphocytes (CD4 T cells) mainly and the cells of the macrophage-monocyte lineage. Depletion or dysfunction of these cells leads to immunodeficiency. CD4 is also expressed by microglia, astrocytes, oligodendroglia and villus Hofbauer cells (placenta), whose functional impairment also contributes to HIV disease.

On inoculation via mucosal route, the HIV traverses through the submucosa and spreads to draining lymph nodes via infection of CD4+ CCR5+ cells, establishing viral reservoirs. During this initial period of 10 days (*eclipse phase*), the virus cannot be detected in the peripheral blood. The infected CD4 lymphocytes proliferate in the lymphoid tissues leading to generalized lymphadenopathy (*acute retroviral syndrome*). The HIV replication reaches a threshold within the next 3–6 weeks of infection, following which there is a burst of viremia in the plasma characterized by *flu-like* symptoms (fever, rash, lymphadenopathy, arthralgia, etc.). Thereafter, there is decrease in the blood viral loads and subsequent steady state within 6–12 months of primary infection. Children do have higher peaks of viremia and a longer acute phase compared to adults.

Thereafter, the patient enters a clinical phase of latency up to 8–12 years, during which high viral turnover and CD4+ lymphocyte depletion continues. Infected monocytes may act as reservoirs of HIV and effectors of tissue damage. There is slow and progressive decline in the CD4 count (direct viral killing of infected cells, increased apoptosis and killing of infected cells by CD8 cytotoxic lymphocytes), whereby the immunocompromised host is rendered susceptible to various opportunistic infections (OIs). Progression of the disease is related to gradual disruption of lymph nodes with loss of its ability to restrict the virus. During later stages, the virus recirculates following gradual disruption of lymph nodes, producing high level of viremia and a rapid decline of CD4+ T cells.

Older children or those with end stage disease may eventually show lymphopenia.

MODES OF TRANSMISSION

Human immunodeficiency virus infection is transmitted by vertical transfer from mother to child; parenteral exposure to infected blood or blood products (especially in those who undergo multiple blood/blood-product transfusions); needle-sharing by drug abusers (in adolescents); and by unprotected sexual contact (in adolescents and adults).

Most new cases in *pediatric population* are through vertical (mother to child) transmission. This vertical transfer of HIV infection can be during *pregnancy* (in 5–10%), during *labor* (in 10–15%) or due to *breastfeeding* (in 5–20%). Breastfeeding assumes an important route of transmission in developing countries as the risk of transmission increases from 15–25% to 20–35% (with breastfeeding for 6 months) and even up to 30–45% (with prolonged breastfeeding for 18–24 months). The risk of HIV transmission with mixed feeding is even higher.

The *predisposing factors* which increase the risk during vertical transmission are preterm delivery (less than 34 weeks), antenatal low maternal CD4 levels, illicit drug use in pregnancy, ruptured membranes (more than 4 hours), low birth weight, high maternal viral loads and advanced disease in mother. The transmission can be reduced by elective cesarean section and ART to the mother and child.

CLINICAL FEATURES

Human immunodeficiency virus has a broad spectrum of *manifestations* ranging from nonspecific to specific symptoms and signs. It is a multiorgan disease. Children present differently from adults. This is mainly due to their immature and developing immunity, which allows dissemination amongst all the organ systems. Three clinical patterns were described in children [before the introduction of highly active antiretroviral therapy (HAART)]—*rapid, short-term and long-term progressors*. *Rapid progressors* (15–25%) have onset of AIDS within first few months of life and median survival of 6–9 months (if untreated). They are common in HIV-infected newborns in developing countries and present with OIs and neurological manifestations. *Short-term progressors* (60–80%) are seen amongst majority of perinatal infections (mainly intrapartum transmissions). They present with HIV related illness by 3–4 years and progress to AIDS later (by 6–7 years); median survival being 6 years. They commonly present with recurrent bacterial infections, failure to thrive and lymphoid interstitial pneumonitis (LIP). *Long-term progressors* (<5%) have minimal or no disease progression and are amongst few with perinatal infection. Their relatively normal CD4 counts, very low viral loads (for longer than 8 years) and delayed manifestations (median survival of 12–13 years) are probably due to effective humoral immunity, cytotoxic T lymphocytic response, host genetic factors or infection with attenuated/defective virus.

The *clinical presentation* also varies amongst infants, children and adolescents. Infants commonly present with lymphadenopathy, hepatosplenomegaly, recurrent gastrointestinal infections, oral thrush and opportunistic infections like *Pneumocystis jiroveci* pneumonia (PCP), and cytomegalovirus (CMV). Beyond infancy, children may present with growth failure, fever, diarrhea and secondary infections. Older children show growth failure, delayed puberty, mild cognitive dysfunction, cardiomyopathy and idiopathic thrombocytopenic purpura (ITP). An entity of *congenital HIV syndrome* has also been described—consisting of microcephaly, prominent box-like forehead, flattened nasal

bridge, short nose with flattened columella, well-formed triangular philtrum and patulous lips with prominent upper vermillion border.

In comparison to developed countries, resource poor settings differ by the presence of additional problems like malnutrition and recurrent infections, which itself influence progression of the disease. Clinical presentation in developing world is unique as compared to developed nations and measles, tuberculosis, varicella, PCP, acute/persistent/recurrent diarrhea, neurological manifestations, contribute to the morbidity and early mortality.

Various classifications have been used in HIV disease for the baseline assessment of the patient, identification of severity of the illness, and decision regarding treatment and prophylaxis. The commonly used classifications are the *Revised CDC Classification* (1994), the *Immune Classification* (Table 1) and the *WHO Clinical Staging* (revised in 2006) (Box 1). Only the common and important manifestations are mentioned in the Box 1.

Children with HIV are commonly diagnosed with the following clinical presentations—failure to thrive (50–70%), hepatosplenomegaly (40–70%), anemia (40–50%), fever (30–60%), lymphadenopathy (40%), coinfection with tuberculosis (TB) (30–50%), diarrhea (20–30%), candidiasis (20%) and central nervous system (CNS) symptoms (5–15%). The organ specific manifestations are described in Table 2. Of the respiratory manifestations, lymphoid interstitial pneumonitis (LIP) needs special mention and is described here.

Table 1 Revised US Centers for Disease Control and Prevention (CDC) Classification (1994) of human immunodeficiency virus (HIV) in children less than 13 years and immune classification (based on absolute CD4 counts or percentage)

<i>Revised CDC clinical categories of HIV in children <13 years (1994)</i>	<i>Immune classification (Based on absolute CD4 counts/percentage of CD4 cells)</i>
<i>Category N: Not symptomatic</i>	<i>Not significant:</i> <11 months (%): >35 12–35 months (%): >30 36–59 months (%): >25 >5 years (cells/mm ³): >500
<i>Category A: Mildly symptomatic</i> More than two of following (but not of category B/C)—Lymphadenopathy, hepatosplenomegaly, dermatitis, parotitis, recurrent or persistent URI, sinusitis, otitis media.	<i>Mild:</i> <11 months (%): 30–35 12–35 months (%): 25–30 36–59 months (%): 20–25 >5 years (cells/mm ³): 350–499
<i>Category B: Moderately symptomatic</i> Symptoms other than those in A or C—anemia/neutropenia/thrombocytopenia persisting >30 days, candidiasis, cardiomyopathy, CMV (onset before 1 month age), hepatitis, recurrent/chronic diarrhea, etc.	<i>Advanced:</i> <11 months (%): 25–29 12–35 months (%): 20–24 36–59 months (%): 15–19 >5 years (cells/mm ³): 200–349
<i>Category C: Severely symptomatic</i> Multiple recurrent serious bacterial infections, disseminated coccidioidomycosis, extrapulmonary cryptococcosis, encephalopathy, disseminated histoplasmosis, Kaposi's sarcoma, etc.	<i>Severe:</i> <11 months (%): <25 12–35 months (%): <20 36–59 months (%): <15 >5 years (cells/mm ³): <200

Abbreviations: CMV, cytomegalovirus; URI, upper respiratory infection.

BOX 1 World Health Organization (WHO, 2006) clinical staging of human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS) in children below 15 years

Clinical stage 1: Asymptomatic/persistent generalized lymphadenopathy.
Clinical stage 2 (mild): Unexplained persistent hepatosplenomegaly, recurrent or chronic upper respiratory tract infections, herpes zoster, persistent parotid enlargement, etc.

Clinical stage 3 (advanced): Unexplained moderate malnutrition or wasting, persistent fever, persistent diarrhea, persistent oral candidiasis, unexplained anemia or neutropenia or thrombocytopenia, lymph node- or pulmonary-tuberculosis, recurrent bacterial pneumonia, bronchiectasis, etc.

Clinical stage 4 (severe): Unexplained severe malnutrition or wasting, recurrent severe bacterial infections, *Pneumocystis jiroveci* pneumonia (PCP), extrapulmonary tuberculosis, cytomegalovirus (CMV) organ infection, esophageal or tracheobronchial or lung candidiasis, central nervous system (CNS) toxoplasmosis, HIV encephalopathy or HIV cardiomyopathy or HIV nephropathy, etc.

Lymphoid Interstitial Pneumonitis

Lymphoid interstitial pneumonitis is a noninfectious lymphoproliferative pathology and is seen in up to 30–40% of all respiratory disorders in HIV-infected children. It indicates immunological deficiency due to the HIV disease. There is infiltration of mature CD8 lymphocytes, plasma cells and histiocytes in the interstitial parenchyma of the lung, alveolar septae and lymphatics with pulmonary lymphoid tissue hyperplasia (PLH). The pathogenesis has been attributed to an atypical response by a dysregulated immune system (due to HIV infection) to an inhaled or circulated antigen. The clinical manifestations may range from asymptomatic to severe pulmonary insufficiency. The onset is usually in the 2nd or 3rd year of life and the disease is often insidious and slowly progressive. Clinical presentation may be with cough, fatigue, dyspnea, generalized nonmatted symmetrical lymphadenopathy, bilateral chronic parotid enlargement, clubbing, hepatosplenomegaly, etc. However the course, though variable, is generally benign with prolonged survival. Advanced

stages of disease may show oxygen desaturation with cyanosis. The diagnosis is largely clinical. Chest radiograph consist of diffuse bilateral reticulonodular infiltrates (lower more than upper zones) and mediastinal/hilar lymphadenopathy. Raised serum IgG level (more than 2,500 mg/dL) has strong association with LIP. Confirmation of interstitial pattern and monitoring of the extent and severity of the disease can be done by high-resolution computed tomography (HRCT) of the chest. Lung biopsy establishes definite diagnosis, but is rarely used in pediatric practice. The treatment of LIP consists of systemic corticosteroids (prednisolone at 1–2 mg/kg/day) for severe disease with significant hypoxemia and respiratory insufficiency (given for 2–4 weeks with gradual tapering). In refractory cases, lowest possible steroid dose can be continued for 4–6 months.

OPPORTUNISTIC INFECTIONS

Opportunistic infections are the hallmark manifestations of immunodeficiency disorders like HIV. Children with HIV show a gradual decline in (both humoral and cell mediated) immunity, thereby making them increasingly susceptible to OIs. These OIs can be bacterial, fungal, viral or protozoal. One should be able to prevent, diagnose and treat these infections at the earliest to reduce morbidity and mortality in the HIV infected patients. It is important to have a high index of suspicion for clinical diagnosis of these OIs, as all the diagnostic tests may not be available/affordable in developing countries like India.

Pneumocystis carinii (jiroveci) Pneumonia

It is the most common OI in infants, with a high mortality (which may go up to 35%). By 4 years of age, over 80% of children acquire serum antibodies and manifestations in immunocompetent children may be mild to asymptomatic. The incidence in HIV-infected children is highest in the first year, peaking at about 3–6 months of age. The clinical diagnosis in infancy needs a high index of suspicion. HIV-infected children usually present with an acute tetrad of fever, tachypnea, dyspnea and cough. The second peak incidence of PCP is when the CD4 counts fall to less

Table 2 Organ specific manifestations in children with human immunodeficiency virus (HIV)

Organ system	Manifestations	Etiopathogenesis	Diagnosis and treatment
Respiratory system (Figures 1 and 2)	Recurrent upper and lower respiratory tract infections, invasive sinusitis, mastoiditis, bronchiectasis, etc.	<i>Pneumocystis carinii</i> pneumonia (PCP), <i>S. pneumoniae</i> , <i>H. influenzae</i> , <i>P. aeruginosa</i> , Viruses (CMV), Fungi (<i>Candida</i> , <i>Aspergillus</i> , <i>Histoplasma</i> , <i>Cryptococcus</i>), Tuberculosis, Lymphoid interstitial pneumonitis (LIP)	Specific to organism
Central nervous system Primary involvement (HIV neurotropic) seen in 50–90% of perinatal infections in developing regions	Static encephalopathy (25%) as developmental delay, Progressive encephalopathy as neuroregression, microcephaly, symmetrical motor dysfunction, apathy, spasticity, hyper-reflexia, abnormal plantar reflex, gait abnormalities, loss of language and motor skills, etc. Older children—scholastic backwardness, cognitive deterioration, learning disabilities, behavioral problems, cerebrovascular complications, etc.	HIV virus induced neoplasms secondary to immunodeficiency, OIs (TB, <i>Toxoplasma</i> , CMV, JC virus, HSV, <i>Cryptococcus</i> , etc.), and adverse effects of drugs	Neuroimaging: • Cerebral atrophy • Enlargement of ventricles • Basal ganglia calcifications • Leukomalacia • Early treatment in encephalopathy with highly active antiretroviral therapy (HAART) with drugs with good CNS penetration (zidovudine/stavudine/efavirenz) • Rule out comorbid pathology (OIs/stroke/CNS tumor) in case of focal neurological signs or seizures

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Organ system	Manifestations	Etiopathogenesis	Diagnosis and treatment
Gastrointestinal and hepatic disease	<p>Oral and esophageal lesions, periodontal disease, salivary gland disease (chronic parotid enlargement in 15%), oral hairy leukoplakia, oral ulcers, recurrent or chronic diarrhea, malabsorption, abdominal pain, dysphagia and failure to thrive.</p> <p>HIV or AIDS enteropathy (Malabsorption due to partial villus atrophy by direct HIV infection of gut).</p> <p>Hepatomegaly</p> <p>Chronic hepatitis, portal hypertension, liver failure</p> <p>Pancreatitis</p>	<p>Bacteria (<i>Salmonella</i>, <i>Campylobacter</i>, <i>Mycobacterium avium</i> intracellulare—MAC, <i>M. tuberculosis</i>), Protozoa (<i>Giardia</i>, <i>Cryptosporidium</i>, <i>Isospora</i>, <i>Microsporidia</i>), Viruses (CMV, herpes simplex virus, rotavirus), or fungi (<i>Candida</i>)</p> <ul style="list-style-type: none"> • Viral replication in reticuloendothelial system • Hepatitis B (with Hepatitis D coinfection) or hepatitis C, CMV and MAC <p>Drug induced (pentamidine, didanosine, lamivudine) or OIs (MAC, CMV, PCP, <i>Cryptosporidium</i>)</p>	<p>Proper nutrition essential in failure to thrive.</p> <p>Serum transaminases fluctuations with/without cholestasis (often drug induced)</p>
Cardiovascular system	<p>Dilated cardiomyopathy, coronary artery disease/arterial hypertension, left ventricular hypertrophy, isolated right ventricular and pulmonary disease, pulmonary hypertension and congestive cardiac failure can occur. Resting sinus tachycardia or sinus arrhythmia, pericardial effusion, cardiac tamponade, conduction disturbances, nonbacterial thrombotic endocarditis, and sudden death may be seen</p>	<p>Prolonged immunosuppression, opportunistic infections (OIs), viral infections, nutritional deficiencies, immune-mediated reactions and adverse effects of drug therapy (zidovudine)</p>	<p>Electrocardiography and echocardiography are helpful in assessing cardiac function. Supportive treatment is required (diuretics, vasodilators and inotropes)</p>
Renal disease	<p>Acute tubular dysfunction with fluid and electrolyte abnormalities and/or renal failure.</p> <p>HIV associated nephropathy (focal and segmental glomerulosclerosis with mesangiopathies, nephrotic syndrome), Immune mediated glomerulopathies (IgA nephropathy, lupus-like etc.)</p> <p>HIV associated thrombotic mesangiopathies</p>	<p>HIV infection of epithelial cells, immune-complex mediated, OIs, hyperviscosity (hyperglobulinemia) or use of nephrotoxic drugs (indinavir causing tubulointerstitial nephritis, acute renal failure and renal calculi)</p>	<p>Treatment is with HAART and angiotensin-converting enzyme inhibitors. Nephrotic syndrome is the most common manifestation of pediatric renal HIV disease. Cases resistant to steroid therapy can be candidates for cyclosporine therapy</p>
Dermatological disorders: Severe, recurrent, persistent and resistant	<p>Exclusive to HIV—oral hairy leukoplakia, bacillary angiomatosis, Kaposi's sarcoma</p> <p>Greater frequency/severe in HIV—Seborrheic dermatitis, severe eczema, psoriasis, drug eruptions, aphthous ulcers, HSV, herpes zoster, molluscum contagiosum, anogenital warts, candidal infections, tinea, onychomycosis, impetigo and scabies</p>	<p>Inflammatory or infectious disorders which are not necessarily unique to HIV infection</p>	<p>The disorders tend to be more disseminated and respond less consistently to conventional therapy</p>
Hematological manifestations	<p>Anemia (20–70%)</p> <p>Leukopenia (seen in one-third, commonly neutropenic)</p> <p>Thrombocytopenia (20%)</p> <p>Thrombosis</p>	<p>Chronic infection, inadequate nutrition (folic acid, vitamin B₁₂ or micronutrient deficiency), autoimmune factors, virus-associated conditions (hemophagocytic syndrome or parvovirus B19 red cell aplasia), Bone marrow suppression or due to adverse effect of drugs (zidovudine).</p> <p>Drugs used for treatment or OI prophylaxis or antiretroviral drugs (zidovudine).</p> <p>It may immunologic (i.e., circulating immune complexes or antiplatelet antibodies), or due to drug toxicity or idiopathic.</p> <p>Hyperviscosity (hypergammaglobulinemia), protein C and protein S deficiency</p>	<p>In low erythropoietin levels, subcutaneous recombinant erythropoietin may be useful.</p> <p>Antineutrophil antibodies are the cause, treatment with intravenous immunoglobulin (IVIg) is useful, subcutaneous granulocyte colony-stimulating factor can be used.</p> <p>Treatment with IVIG or anti-D offers some improvement. If ineffective, a 2–3 days course of high-dose steroids is an alternative. ART can also reverse the thrombocytopenia</p> <p>Clinical disease due to arterial or venous thrombosis rare</p>

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Organ system	Manifestations	Etiopathogenesis	Diagnosis and treatment
Malignancies	Non-Hodgkin lymphoma and primary CNS lymphoma Kaposi's sarcoma	Epstein-Barr virus Human herpes virus 8	Chemotherapy and ART
Other organs	HIV—arthropathy, myopathy, rheumatologic, endocrine and metabolic disorders	—	Symptomatic treatment and ART
Growth, nutrition and endocrine system	Growth delay, Delayed puberty, HIV associated lipodystrophy, lipoatrophy, hyperlipidemia, Insulin resistance, hyperinsulinemia, hyperglycemia	Infections, altered gastrointestinal and metabolic functions, drugs, antiretroviral medications, malnutrition	Nutritional assessment in all patients, counseling and education, 1–5 times recommended intake of vitamins and minerals, oral supplements/enteral tube feedings/parenteral nutrition

Abbreviations: PCP, *Pneumocystis carinii* pneumonia; CMV, cytomegalovirus; LIP, lymphoid interstitial pneumonitis; TB, tuberculosis; HSV, herpes simplex virus; HAART, highly active antiretroviral therapy; CNS, central nervous system; OI, opportunistic infection; MAC, *Mycobacterium avium* intracellulare, IVIG, intravenous immunoglobulin.

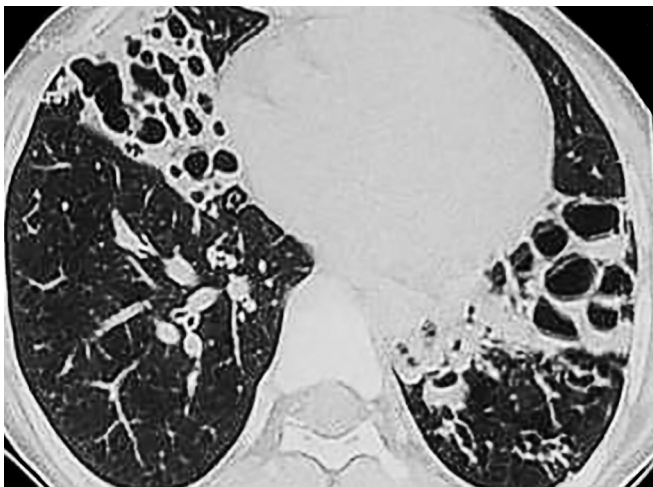


Figure 1 High-resolution computed tomography (HRCT) chest showing bilateral bronchiectatic changes in a human immunodeficiency virus (HIV) infected child

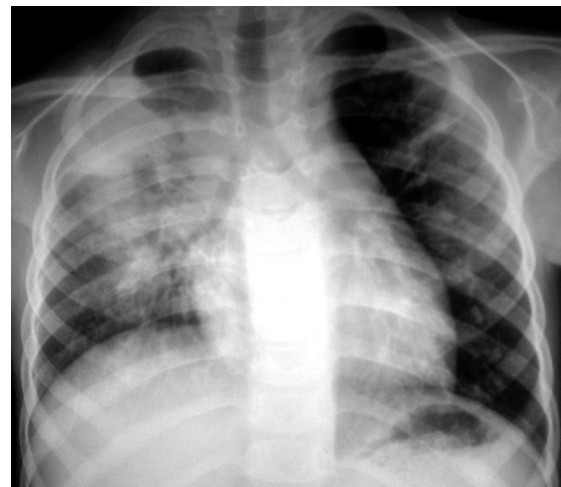


Figure 2 Chest radiograph showing bilateral extensive lobar consolidation (pneumonia) in a human immunodeficiency virus (HIV) infected child



Figure 3 Chest radiograph of *Pneumocystis jirovecii* pneumonia (PCP) showing bilateral diffuse parenchymal infiltrates

than 200 cells/mm³ or less than 14% due to new infection or an activation of a latent infection. Insidious onset cough and dyspnea may be seen in older children. Clinical features and differential

diagnoses of PCP are discussed in Chapter 33.9 on *Pneumocystis jirovecii* (**Fig. 3**). *P. carinii* (*jirovecii*) can be demonstrated from induced sputum samples (50% sensitivity; 90% specificity) or less commonly in bronchoalveolar lavage (BAL) samples (90% sensitivity; 99% specificity even at 72 hours after treatment initiation), fiberoptic bronchoscopy with transbronchial biopsy (if BAL is negative) and open lung biopsy. PCP is treated with IV trimethoprim-sulfamethoxazole; steroids are given in severe cases (See Chapter 33.9 for details of treatment of PCP). If child does not improve within 4–7 days, it is prudent to consider other etiologies, coinfections (with other organisms like pneumococcus or CMV) and treatment failure. Surfactant therapy may be considered as last option in severely ill infants. Cotrimoxazole (TMP-SMX) prophylaxis reduces the incidence of PCP infection (dose: 6 mg/kg/day of TMP). TMP-SMX also protects against development of infections by other bacteria, malaria, *Isospora*, *Cyclospora* as well as toxoplasmosis, besides reducing the mortality in children. The 2009 WHO Guidelines for cotrimoxazole use are described in **Table 3**.

Tuberculosis

Human immunodeficiency virus infected children are at a high risk of TB with up to 48% having culture proven TB. The disease tends to be more severe, extrapulmonary, drug resistant and

Table 3 The 2009 World Health Organization (WHO) guidelines for cotrimoxazole for *Pneumocystis carinii* pneumonia (PCP) prophylaxis in children

<i>All HIV exposed infants</i>	Start 4–6 weeks of age after birth and continued for at least 6 weeks after cessation of risk of HIV transmission (breastfeeding) and definitive exclusion of HIV infection in infant	Once a child is started on cotrimoxazole, prophylaxis should be continued until 5 years of age regardless of clinical symptoms or CD4 percentage. Specifically, infants who begin cotrimoxazole prophylaxis before the age of 1 year and are subsequently asymptomatic and/or have CD4 levels >25% should remain on cotrimoxazole prophylaxis until they reach the age of 5 years
<i>HIV-infected children</i>		
<1 year	Used in all, regardless of CD4 percentage or clinical status	
1–4 years	Prophylaxis required if the child has WHO clinical stages 2, 3 or 4, regardless of CD4 percentage or if the child has CD4 percentage below 25% at any WHO stage	
>5 years	WHO clinical stage 2, 3 and 4 (if CD4 counts are not available) or WHO clinical stage 3 and 4 (irrespective of CD4 counts) or if CD4 count <350 cells/mm ³ irrespective of WHO staging	Children older than 5 years can be reassessed and consideration given to discontinuing cotrimoxazole prophylaxis after sustained immune reconstitution in accordance with the recommendations for adults and adolescents
OR		
<i>Universal option:</i> Prophylaxis for all infants and children born to mothers confirmed to be or suspected of living with HIV. This strategy may be considered in settings with a high prevalence of HIV, high infant mortality due to infectious diseases and limited health infrastructure.		
<i>Previous infection with PCP</i>	Secondary cotrimoxazole prophylaxis has the same regimen as recommended for primary prophylaxis	The general recommendation is that secondary cotrimoxazole prophylaxis should not be discontinued, irrespective of the clinical and immune response to ART

Abbreviations: PCP, *Pneumocystis carinii* pneumonia; HIV, human immunodeficiency virus; ART, antiretroviral therapy.

associated with atypical mycobacteria. Younger children present commonly with localized pulmonary involvement with hilar adenopathy, extrapulmonary and miliary TB, while older children and adolescents may show cavitary TB. Drug sensitivity testing should be done in positive cultures especially in treatment failures and relapses. Antitubercular therapy (ATT) should be started as per standard guidelines with prolongation of the course if needed. ART should be started in any child with active disease as soon as possible and within 8 weeks following initiation of antituberculous treatment irrespective of CD4 count and clinical stage. It should be remembered that rifampicin induces increased hepatic clearance of protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs). The concomitant use of rifampicin with efavirenz and nevirapine also requires dose adjustments. Children living with HIV should regularly be screened for symptoms of poor weight gain, fever or current cough or contact history with a TB case. If they are more than 12 months old, 6 months of isoniazid preventive therapy (IPT) at 10 mg/kg/day should be given as part of comprehensive package of HIV prevention and care services if they are unlikely to have active TB on screening and have no TB contact. In HIV-infected children less than 12 months of age, IPT should be offered to only those with contact with TB case if evaluation (using investigations) shows no TB disease.

Recurrent Bacterial Infections

Common bacterial infections seen in HIV-infected children are pneumonia, sepsis, bacteremia, abscesses, meningitis, osteomyelitis, septic arthritis, otitis media, etc. These are caused by organisms like *Streptococcus pneumoniae*, *Haemophilus influenzae* type *b* (Hib), *Staphylococcus aureus*, *Escherichia coli*, *Pneumococcus*, etc. The clinical presentation and treatment is essentially similar to that in the non-HIV infected children; however the disease may be chronic/severe and longer duration of antibiotics may be necessary. Prophylaxis with TMP-SMX, routine as well as special vaccinations (pneumococcal and Hib vaccines) and screening can reduce the incidence of bacterial infections.

Mycobacterium avium Complex (MAC)

These are non-tuberculous mycobacteria [i.e., *M. avium* (predominantly a disseminated disease), *M. intracellulare* (predominantly

respiratory manifestations) and *M. paratuberculosis*] and are seen frequently in children with low CD4 counts (less than 50 cells/mm³), high plasma HIV-RNA levels (more than 100,000 copies/mL), previous OIs and previous colonization of the respiratory and gastrointestinal tract. MAC can present as isolated lymphadenitis or with involvement of lungs, liver, spleen, bone marrow and gastrointestinal tract. Disseminated MAC infection usually presents in children with advanced HIV disease. Common presentations are—recurrent fever, failure to thrive, night sweats, fatigue, chronic diarrhea and recurrent abdominal pain. The diagnosis is by isolation or culture of organism from blood or biopsy specimen. DNA probe assays can be used for species differentiation. Associated laboratory findings such as anemia (disproportionate to stage of HIV), neutropenia, leukopenia and elevated serum alkaline phosphatase may also be seen. The treatment includes a combination of two or more drugs and therapy is recommended for at least 18 months. Clarithromycin (7.5–10 mg/kg/day PO BD) or azithromycin (10–12 mg/kg/day PO OD) with ethambutol (15–20 mg/kg/day PO OD) can be used. Alternative drugs are ciprofloxacin, amikacin or streptomycin. Disseminated disease requires 3–4 drugs combination to be given till there is improvement followed by two drug therapy. Primary prophylaxis with clarithromycin or azithromycin is required when the CD4 count is less than 50 cells/mm³ in children more than 6 years age, less than 75 cells/mm³ in 1–6 year age group and less than 500 cells/mm³ in less than 1 year of age. Secondary prophylaxis with clarithromycin (or azithromycin) and ethambutol is recommended in diagnosed cases of MAC.

Candidiasis

Candida is the most common fungal infection in HIV-infected children. Oral thrush is most common and recurrent presentation is one of the clinical indicators of HIV in infants more than 8 weeks of age. Esophageal candidiasis is an AIDS-defining condition with increased occurrence in patients with low CD4 counts (less than 100 cells/mm³), high viral load, neutropenia and concomitant oropharyngeal candidiasis. Systemic candidiasis may occur with prolonged use of antibiotics and can also manifest as endophthalmitis, shock or sepsis (also see Chapter 33.3 on Candidiasis). The treatment of oral thrush is topical clotrimazole

(4–6 hourly for 1–2 weeks) or oral nystatin suspension. Oral fluconazole, itraconazole or ketaconazole can be used if topical therapy fails. For esophageal candidiasis, the treatment is with intravenous fluconazole (3–6 mg/kg/day for 21 days) which can be made oral once child can swallow food. For treatment of systemic candidiasis, amphotericin B (0.5–1.5 mg/kg OD IV over 1–2 hours) has to be given for 14–21 days (after resolution of signs

and symptoms and last positive blood culture). Flucytosine can be added in severe invasive disease. *Prophylaxis* is recommended with fluconazole (3–6 mg/kg PO OD) or itraconazole (5 mg/kg PO OD) in cases with severe mucocutaneous or esophageal candidiasis and can be stopped once the CD4% is more than 15% on more than two occasions (on ART). **Table 4** summarizes the OIs seen in HIV-infected children.

Table 4 Opportunistic infections (OIs) in children with human immunodeficiency virus (HIV)

<i>Infection/pathogen</i>	<i>Clinical findings/organ involvement</i>	<i>Diagnosis</i>	<i>Treatment and prophylaxis</i>
Cytomegalovirus (CMV): 8–10% of pediatric AIDS defining illness	<i>CMV retinitis</i> : Most common, usually asymptomatic. Lungs, liver, GI tract, pancreas, sinuses and CNS	<i>Fundoscopy</i> : White and yellow retinal infiltrates and retinal hemorrhages. <i>Histology</i> : Owl eye intranuclear and intracytoplasmic inclusion bodies. Staining with CMV monoclonal antibodies. <i>Serology</i> : Not very useful but negative IgG makes CMV disease unlikely. <i>CMV—Antigenemia (acute or latent infection)</i> : Viral matrix protein pp65 on infected neutrophils. Viral cultures, CMV DNA PCR.	Ganciclovir for 14–21 days or foscarnet followed by lifelong maintenance therapy with ganciclovir. Fundoscopy every 6 monthly in all HIV children. <i>Prophylaxis</i> : Primary-Ganciclovir in HIV children with severe immunosuppression (CD4 <50 cells/mm ³). Secondary-Ganciclovir.
HSV (Herpes simplex virus) Vertical or horizontal transmission. *HSV ulcers >1 month VZV (Varicella/Herpes Zoster virus)	Neonatal (usually HSV2): CNS, skin, eyes or mouth. Beyond neonatal age: Extensive orolabial ulcers (gingivostomatitis), genital ulcers, encephalitis or systemic disease. Severe infection, mucosal involvement, systemic spread: pneumonia, hepatitis, encephalitis, retinitis.	Ulcers are clinically diagnostic. Virus isolation in culture, immunofluorescence staining of HSV 1 and HSV2 antigens from skin and mucosal scrapings, detection of HSV DNA by PCR in CSF in HSV encephalitis. Tzanck smear from cell scrapings, VZV antigen in lesions, Viral isolation from culture, PCR.	Acyclovir. Neonatal CNS disease—21 days. Other involvement in neonates, post neonatal CNS, gingivostomatitis: 14 days. <i>Prophylaxis</i> : Not recommended. Prevent exposure. Isolation and oral or intravenous acyclovir for 7–14 days. Intravenous foscarnet in resistant cases. Prophylaxis-Varicella immunoglobulin within 96 hours of exposure.
Toxoplasmosis	Most asymptomatic, CNS toxoplasmosis often with ocular involvement.	Neuroimaging (Fig. 4): Ring-enhancing lesions in basal ganglia, corticomedullary junction, granulomas, calcification. CSF IgG antibodies.	Pyrimethamine-Sulfadiazine with folinic acid. Alternative-clindamycin, azithromycin, or TMP-SMX. Steroids if severe chorioretinitis or CNS involvement with mass effect. <i>Prophylaxis</i> : Primary-TMP-SMX used for PCP prophylaxis protects. Secondary-Sulfadiazine (or clindamycin)-pyrimethamine with folinic acid. Avoid exposure to cat feces, proper hand washing and avoid uncooked or raw meat ingestion.
<i>Cryptococcus neoformans</i>	Meningitis is most common. Others—bones, joints, skin, lungs. Severely immunocompromised children between 6 years and 12 years are more prone.	CSF examination—may be normal, but elevated opening pressure, India ink preparation, cultures, cryptococcal antigen (useful for response to treatment).	<i>Induction</i> : Amphotericin B with/without flucytosine for 2 weeks. <i>Consolidation</i> : Fluconazole for 8–10 weeks or Itraconazole for 2 weeks. <i>Prophylaxis (only secondary)</i> : fluconazole lifelong or till CD4 improves to 100–200 cells/mm ³ (adolescents on ART).
Histoplasmosis	Acute pneumonia, meningitis Progressive disseminated histoplasmosis (in CD4 ≤150 cells/mm ³) presents with prolonged fever, failure to thrive, pneumonitis, hepatosplenomegaly, lymphadenopathy.	Cultures, histopathology, serology, antigen detection (serum, BAL, CSF with 100% sensitivity), PCR.	Amphotericin B Secondary prophylaxis-oral itraconazole for 1 year.

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Infection/pathogen	Clinical findings/organ involvement	Diagnosis	Treatment and prophylaxis
Penicilliosis* Seen in North–East India	Persistent fever, anemia, thrombocytopenia, skin lesions (translucent umbilicated papules–face, ears, extremities), hepatomegaly, generalized lymphadenopathy.	Wright staining of skin scrapings–basophilic, spherical yeast like with central septation. Isolation from blood, bone marrow, etc.	Amphotericin B intravenous for 2 weeks followed by oral itraconazole for 10 weeks. Secondary prophylaxis (only)–Itraconazole.
<i>Isospora belli</i> and <i>Cyclospora</i>	Chronic diarrhea	Stool microscopy, antigen detection	TMP-SMX
<i>Microsporidia</i>	Chronic diarrhea	Stool microscopy, antigen detection	Albendazole or Nitazoxanide
<i>Cryptosporidia</i>	Acute or persistent diarrhea. Complications–cholecystitis, cholangitis, hepatitis, pancreatitis, severe malabsorption	Stool microscopy, staining and antibody detection	Fluid rehydration. Nitazoxanide or Azithromycin

Abbreviations: HSV, herpes simplex virus; PCR, polymerase chain reaction; CSF, cerebrospinal fluid; CNS, central nervous system; VZV, Varicella/Herpes Zoster virus; CMV, cytomegalovirus; TMP-SMX, trimethoprim-Sulfamethoxazole; ART, antiretroviral therapy; BAL, bronchoalveolar lavage.

*AIDS defining illness



Figure 4 Magnetic resonance imaging (MRI) brain of toxoplasmosis showing well defined peripherally enhancing lesion with surrounding perilesional edema in right gangliocapsular region with mass effect

DIAGNOSIS OF HIV INFECTION

It can be done by virological or serological methods (if more than 18 months age). Presumptive diagnosis can also be made by certain clinical criteria in children less than 18 months where virological methods are unavailable. These methods are further described in **Table 5**. The WHO recommendations are summarized in **Table 6**.

MANAGEMENT OF HIV INFECTION

The management of HIV disease has changed dramatically after the availability of effective ART. ART cannot cure HIV infection but it helps in achieving an acceptable quality of life, normal growth and development and minimizes morbidity due to OIs and organ involvement. Antiretroviral regimens available now-a-days are safer, simpler to follow, efficacious and affordable than before. ARTs are potent inhibitors of viral replication, which by reducing viral burden; make the disease a chronic illness. ART should be administered under the guidance of an expert in pediatric HIV disease. The basics of ART are summarized in **Tables 7** and **8**. The indications for starting ART and WHO first-line regimen is

described in **Table 9** while other general aspects of health-care and management in children with HIV infection are summarized later.

Monitoring

All HIV patients (with/without ART) should undergo clinical and laboratory monitoring for disease activity and response to treatment. Complete hemogram, liver functions, urine and stool examination, fundoscopy, echocardiography (ECG) and height should be monitored annually and CD4 counts every 3–6 monthly. At each visit healthcare provider should assess immunization status, symptoms of OIs, cotrimoxazole prophylaxis and concomitant medications and also reassess criteria for ART initiation and evaluate the family situation. While patients on ART should be followed-up monthly, those children not on ART also require regular follow-up.

Counseling

Children of school age should be disclosed their HIV-positive status and their parents or caregiver's status; younger children should be told their status incrementally to accommodate their cognitive skills and emotional maturity (in preparation for a full disclosure). Parents or caretakers should be counseled about the disease and course of the illness. Treatment decisions should be based on adherence, which depends on understanding by caretaker, availability of medicines and accessibility to healthcare and socioeconomic conditions.

Prophylactic Regimens

Pneumocystis carinii (*jiroveci*) pneumonia prophylaxis has already been discussed. Prophylaxis against MAC is required in children with severe immunosuppression (i.e., CD4 lymphocyte count < 500 cells/mm³ in children < 1 year, < 75 cells/mm³ in 1–6 years age, and < 50 cells/mm³ in children > 6 years age) and the drugs of choice are clarithromycin (7.5 mg/kg twice a day orally) or azithromycin (20 mg/kg once a week orally or 5 mg/kg daily orally). Primary prophylaxis against OIs can be discontinued if patients have sustained (> 6 months) immune reconstitution with HAART. Intravenous immunoglobulin (IVIG) (dose 400 mg/kg every 4 weeks) has been recommended to prevent recurrent serious bacterial infections for symptomatic patients who have suffered from at least two documented serious bacterial infections within 1 year; have laboratory-documented inability to make antigen-specific antibodies; or in those who have hypogammaglobulinemia.

Table 5 Diagnosis of human immunodeficiency virus (HIV) in children

Serological tests: <ul style="list-style-type: none">• Detect HIV antibodies• Enzyme immunoassays (EIA), rapid tests, Western Blot• Whole blood, oral fluids (less common)• Passive transfer of maternal IgG HIV antibodies usually disappear by 6–12 months in infants (seroreverters)• Diagnosis established only in infants >18 months of age• If 1st test reactive, diagnosis to be confirmed by 2nd (or 3rd in high prevalence regions) test using different method		Virological tests: Include HIV RNA/DNA by nucleic acid testing-(NAT) or polymerase chain reaction (PCR) and viral proteins (p24). Useful for definitive diagnosis by 1–6 months of age. At 4–6 months of age, the HIV culture or PCR can identify all infected infants. <i>HIV-DNA:</i> Qualitative test: Diagnostic purposes. On whole blood/dried blood spot (DBS). HIV-DNA PCR: About 40% of infected newborns have positive test results in the first 2 days of life, with more than 90% testing positive by 2 weeks of age. <i>HIV-RNA:</i> Quantitative test: Monitoring disease progression and response to ART. On plasma or DBS. <i>Ultrasensitive p24:</i> Enzyme linked immunoassays (EIA). On whole blood/serum.	
Presumptive diagnosis in <18 months of age (where virological testing unavailable): Presumptive diagnosis of severe HIV disease if: HIV antibody positive confirmed			
AND			
Two or more of following: <ul style="list-style-type: none">• Oral thrush• Severe pneumonia• Severe sepsis <i>Other supportive factors for diagnosis:</i> <ul style="list-style-type: none">• HIV-related maternal death• Advanced HIV disease in mother• CD4 count (child) <20%		OR	Diagnosis of AIDS indicator condition(s): Pneumocystis pneumonia, cryptococcal meningitis, severe wasting or severe malnutrition, esophageal candidiasis, Kaposi sarcoma, extrapulmonary tuberculosis
<i>Diagnosis of HIV infection should be confirmed by virological testing as early as possible.</i>			
Testing protocols			
<i>At Birth and early infancy:</i> Viral diagnostic assay should be done within 48 hours of birth. If negative at 2 days in HIV exposed child, repeat tests at 1–2 months and 4–6 months of age. Diagnosis of HIV infection by two positive virological tests from different blood samples. Exclusion of HIV infection by two negative virological tests (with at least one test performed at or after 4–6 months of age).			
<i>Older children:</i> Diagnosis by positive ELISA antibody test, confirmation by Western Blot or repeat ELISA with different kit. In those > 18 months of age, ELISA test has > 99% sensitivity and specificity. In developing regions, 2–3 ELISA tests using different kits can be used to confirm positive report. HIV infection excluded if two or more HIV antibody tests are negative 1 month apart after 6 months of age (excluding patients with hypogammaglobulinemia or clinical HIV disease). If breastfeeding: Repeat antibody test should be negative after 6–8 weeks of complete cessation of breastfeeding to confirm absence of infection.			

Table 6 Summary of recommended testing approaches for infants and children [World Health Organization (WHO)]

<i>WHO Recommendations</i>		
Virological testing preferred in all children < 18 months		
HIV exposed infant (well)	HIV DNA/RNA or ultrasensitive p24	To be performed at 4–6 weeks of age or earliest opportunity thereafter. If positive start ART at earliest and confirm with second specimen
Infant with unknown exposure	Maternal or infant HIV serological test	If exposed—virological test
HIV exposed infant at 9 months (well)	HIV serological test	If seropositive: Confirm with virological test. To repeat if negative and breastfeeding.
Infant/child with signs/symptoms suggesting HIV	HIV serological test	If seropositive: Confirm with virological tests if < 18 months age
On discontinuation of breastfeeding	HIV serological test after 6 weeks or more of breastfeeding cessation	If seropositive: Confirm with virological tests if < 18 months
Child > 18 months	HIV serological test	—

Immunization

These are equally important to prevent infections. An asymptomatic child with mild symptoms should be given all routine vaccinations. In case of symptomatic patients with severe

immunosuppression/AIDS, live vaccines [like varicella/measles-mumps-rubella (MMR)] are contraindicated. Inactivated or killed vaccines preferred to live vaccines (e.g., inactivated polio vaccine instead of oral polio vaccine). Vaccines like Hib, annual influenza

Table 7 Fundamental principles of antiretroviral therapy (ART) in children

Principles	<ul style="list-style-type: none"> • Stabilize OIs before starting ART • Aim to suppress HIV replication to undetectable levels—to minimize selection of antiretroviral-resistant mutants. • Use combination therapy of antiretroviral drugs (ARVs) and strict adherence.
Appropriate drug selection	<ul style="list-style-type: none"> • Three main types of ART drugs (based on mechanism of action): <ul style="list-style-type: none"> – NRTIs (nucleoside reverse transcriptase inhibitors) – NNRTIs (nonnucleoside reverse transcriptase inhibitors) – PIs (protease inhibitors) • Highly active antiretroviral therapy (HAART) refers to a three drug combination <ul style="list-style-type: none"> – Two NRTIs (thymidine analog AZT/ZDV plus nonthymidine analog 3TC) suppress replication in active plus resting cells PLUS – One NNRTI (EFV/NVP) or PI (LPVr or NFV)
Adherence	<ul style="list-style-type: none"> • Deciding factor for initiation of ART and its success • Compliance below 80–90% leads to suboptimal viral suppression and enhances development of drug resistance (particularly with PIs and NNRTIs) • Participation and extreme dedication of family/caretaker essential as medications often unpalatable • Education on drug administration, follow-up visits, relationship of drug adherence to viral suppression and commitment of the family and the child are important in achieving treatment success
Initiation of ART	<ul style="list-style-type: none"> • Though ART is lifelong, the first 6 months are most important. This is due to the need to balance the improvement (clinical, immunological and viral suppression) as against the higher risks of opportunistic infections, IRIS, and early adverse events (especially in first 3 months) • People with advanced HIV disease (severe immunodeficiency and existing coinfections), severely low hemoglobin, low body mass index and very low CD4 counts or severe malnourishment are more prone to complications when initiated on ART
Immune reconstitution inflammatory syndrome (IRIS)	<ul style="list-style-type: none"> • IRIS is a collection of signs and symptoms associated with immune recovery due to response to ART • It can occur in up to 10% of all patients initiated on ART or up to 25% in those with CD4 count below 50 cells/mm³ • Typically within the first few weeks (2–12 weeks) after initiation of ART (but may also present later) • It may present as paradoxical IRIS, when an opportunistic infection or tumor diagnosed is before ART and responsive to therapy after ART starts; or unmasking IRIS, in which a disease not clinically apparent before ART is triggered by ART initiation • To be considered when the presentation cannot be explained by a new infection, expected course of a known infection or drug toxicity • Clinical spectrum is diverse—fever, new events, clinical deterioration of OIs • IRIS may be reported for infectious, non-infectious conditions and tumors • The most serious and life-threatening forms of paradoxical IRIS are TB, cryptococcosis, Kaposi's sarcoma and herpes zoster. Worsening of coexisting infections (flare of Hepatitis B or C) may be seen localized or systemic BCG vaccine-associated IRIS may be seen in HIV infected infants • Risk factors for IRIS include low CD4 + cell count (<50 cells/mm³) at ART initiation, disseminated opportunistic infections or tumors and a shorter treatment duration for OIs before starting ART • IRIS is generally self-limiting, and interruption of ART is rarely indicated. Reassurance is essential to prevent discontinuation or poor adherence to ART • Life-threatening reactions may require suppression of exaggerated inflammatory response by short course of corticosteroids. Prednisolone 0.5–1 mg/kg/day for 5–10 days can be added in moderate to severe cases • Measures such as early diagnosis of HIV and initiation of ART before CD4 falls below 200 cells/mm³, improved screening of OIs (especially TB and Cryptococcus) and optimal management before initiating ART can help to reduce development of IRIS
Monitoring ART	<p>HIV Diagnosis:</p> <ul style="list-style-type: none"> • HIV serology, CD4 count, TB screening • Optional: HBV and HCV serology, screening for STIs and noncommunicable diseases and comorbidities <p>Follow-up (Before ART):</p> <ul style="list-style-type: none"> • CD4 count (6–12 monthly) <p>ART initiation:</p> <ul style="list-style-type: none"> • CD4 count • Optional: Hemoglobin (for AZT), pregnancy test (adolescents), blood pressure, urine dipsticks for glycosuria, estimated glomerular filtration rate and serum creatinine (for TDF) and alanine transaminase (for NVP) <p>On ART:</p> <ul style="list-style-type: none"> • CD4 count (6 monthly) • HIV viral load (6 months after start of ART and 12 monthly thereafter) • Optional: Urine dipstick for glycosuria and serum creatinine (for TDF) <p>Treatment failure:</p> <ul style="list-style-type: none"> • CD4 count, HIV viral load • Optional: HBV serology

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Routine follow-up	<ul style="list-style-type: none">• Review interim history for TB exposure• Assess growth and nutrition• Symptom directed clinical examination• Developmental assessment• Review for concomitant conditions: OIs, TB, etc.• Confirm stage of HIV• Check adherence to treatment• Recalculate ART doses on each visit• Review drug interactions, preventive drugs (Cotrimoxazole, INH)• Discuss findings on each visit• Appropriate referrals• Reinforce ART adherence, nutrition, side effects of drugs, follow-up, etc.• Laboratory tests when needed• Schedule follow up depending on response to ART• Infants: weeks 2, 4, 6, 8 (after starting ART), then every 4 weeks for 1st year• Children: weeks 2, 4, 8, 12 (after starting ART) then 2–3 monthly when child stabilized on ART	
ARV toxicity	<ul style="list-style-type: none">• Rule out concurrent medications and diseases (OIs, IRIS, etc.).	
Adverse reaction based on:	<ul style="list-style-type: none">• Determine seriousness of adverse event:<ul style="list-style-type: none">– Grade 1 (mild): Reassure, no change in ART– Grade 2 (moderate): Continue ART as long as feasible, SOS single drug substitution if no improvement. Stress need to adhere to ART inspite of toxicity in mild/moderate reactions– Grade 3 (severe): Substitute one offending drug, continue rest ART– Grade 4 (severe life-threatening, e.g., Stevens-Johnson syndrome, lactic acidosis, etc.): Immediate discontinuation of all drugs and manage the event. Once patient stabilized reintroduce modified regimen substituting the offending drug	
<ul style="list-style-type: none">• Report of child on ART or caregiver• History or clinical findings• Laboratory tests		
Treatment failure (WHO definitions for decision to switch ART regimens)	Virological failure: (preferred monitoring approach to diagnose and confirm ARV treatment failure). Plasma viral loads (PVL) above 1,000 copies/mL based on two consecutive viral load measurements after 3 months, with adherence support Clinical Failure: New or recurrent clinical event indicating advanced or severe immunodeficiency (WHO clinical stage 3 and 4 except TB) after 6 months of effective treatment Immunological failure: In < 5-year-old: Persistent CD4 levels below 200 cells/mm ³ or < 10% In > 5-year-old: Persistent CD4 levels below 100 cells/mm ³	
Change of ART (due to failure or in toxicity or intolerance to current treatment)		
All drugs to be changed ideally, if not possible at least two drug changed based on resistance mutation genotype or previous ART regimen		
	<i>Preferred regimens</i>	<i>Alternative regimens</i>
If a NNRTI based first-line regimen was used	Boosted PI + 2 NRTIs ABC + 3TC + LPV/r* *ATV/r alternative if > 6 years	ABC + 3TC + LPV/r* TDF + 3TC (or FTC) + LPV/r*
If a PI based first line regimen was used	< 3 years No change unless failure due to lack of adherence due to poor palatability of LPV/r 3 years to < 10 years NNRTI (EFV preferred)+ 3NRTIs AZT (or ABC) + 3TC + EFV	AZT (or ABC) + 3TC + NVP ABC (or TDF) + 3TC + NVP
Adolescents(> 10 years)		
If d4T /AZT used in first-line ART	TDF + 3TC (or FTC) + ATV/r or LPV/r	
If TDF used in first-line ART	AZT + 3TC + ATV/r or LPV/r	
Third-line ART: <ul style="list-style-type: none">• Need to balance benefits versus risks when second line ART fails• Older children and adolescents: use of novel drugs like ETV, DRV and RAL (used in adults) to construct third-line regimen• If not possible, continue tolerated second-line regimen• If ART stopped, symptomatic and pain relief with prevention of OIs		
Resistance	<ul style="list-style-type: none">• Suspected when multiple failed regimen or suboptimal viral load response to therapy• Drug resistance tests measure virus susceptibility in various drug concentrations (phenotype tests) or predicts by mutations identified in HIV genome isolated in patient (genotype tests)• Single mutation can induce high grade resistance in NNRTIs and 3TC• Serial accumulation of multiple mutations required in AZT, ABC, TDF and most PIs• Low level of resistance in ddl and d4T• Drug resistance testing is becoming standard of care and higher treatment success has been noted	
Drug interactions	Amongst antiretrovirals: ZDV and d4T NOT given together ddl and d4T NOT given together EFV NOT with NVP or 3TC	With others: Rifampicin reduces levels of NNRTIs and PIs Antifungals increase levels of NVP, LPV and SQV (sequinavir). Interactions exist with oral contraceptives, lipid lowering agents and anticonvulsants

Abbreviations: OI, opportunistic infections; ART, antiretroviral therapy; BCG, Bacillus Calmette-Guérin (BCG) vaccine; HBV, hepatitis B virus; HCV, hepatitis C virus; INH, isoniazid, PVL, plasma viral loads; AZT/ZDV, zidovudine; NFV, nelfinavir; RTV, ritonavir; ABC, abacavir; ddI, didanosine; FTC, emtricitabine, 3TC, lamivudine, d4T, stavudine, TDF, tenofovir; EFV, efavirenz; ETV, etravirine; NVP, nevirapine; PIs, proteases inhibitors; ATV/r, Atazanavir + ritonavir; DRV, darunavir; LPV/r, lopinavir/ritonavir; RAL, raltegravir.

Table 8 Antiretroviral (ARV) drugs, dosages, adverse effects and substitutions

<i>Antiretroviral drug (class)</i>	<i>Elimination</i>	<i>Formulation</i>	<i>Daily dose</i>	<i>Adverse effects</i>	<i>Suggested first-line ARV substitute</i>
Lamivudine (3TC) (NRTI)	Renal excretion	Oral, syrup available	8 mg/kg in two divided doses	Gastrointestinal symptoms, rash, lactic acidosis, pancreatitis, peripheral neuropathy	—
Zidovudine (AZT/ZDV) (NRTI)	Hepatic metabolism with renal excretion	Oral, syrup available	8 mg/kg or 480 mg/m ² in two divided doses	Severe anemia, leukopenia, pancytopenia, myopathy, lipodystrophy, lactic acidosis or severe hepatomegaly with steatosis Severe gastrointestinal intolerance Headache, liver toxicity	TDF or ABC d4T or ABC
Stavudine (d4T) (NRTI)	50% renal excretion	Oral	2 mg/kg in two divided doses	Lactic acidosis or severe hepatomegaly with steatosis, lipodystrophy, peripheral neuropathy, pancreatitis Headache, nausea, anemia, rash	TDF or AZT or ABC —
Didanosine (ddI) (NRTI)	50% renal excretion	Oral	240 mg/m ² in two divided doses	Gastrointestinal symptoms, peripheral neuropathy, pancreatitis, lactic acidosis	—
Abacavir (ABC) (NRTI)	Hepatic	Oral	16 mg/kg in two divided doses	Hypersensitivity reaction Gastrointestinal symptoms, rash, lactic acidosis, elevated triglycerides, lipodystrophy, pancreatitis	AZT (or TDF or d4T) —
Efavirenz (EFV) (NNRTI)	Hepatic	Oral, syrup available	15 mg/kg (200–400 mg) once a day	Persistent and severe central nervous system toxicity, hepatotoxicity, convulsions, hypersensitivity reactions, potential teratogenicity	NVP If NNRTIs not tolerated-boosted PIs
Nevirapine (NVP) (NNRTI)	Hepatic	Oral, syrup available	120 mg/m ² once daily for first two weeks followed by 240–400 mg/m ² in two divided doses	Severe hepatotoxicity, severe skin rash, hypersensitivity reaction Nausea, headache, fever	EFV. If NNRTIs not tolerated-boosted PIs —
Lopinavir/Ritonavir (LPV/r) (PI)	Hepatic	Oral	450 mg LPV with 115 mg ritonavir/m ² in two divided doses	Hepatotoxicity, pancreatitis, lipoatrophy or metabolic syndrome, dyslipidemia, severe diarrhea	< 3 years- NVP > 3 years- EFV
Nelfinavir (NFV) (PI)	Hepatic	Oral	110–130 mg/kg in two divided doses	Gastrointestinal symptoms, hepatitis, lipid abnormalities	—
Ritonavir (RTV) (PI)	Hepatic	Oral	Begin with 400 mg/m ² and titrate up to 800 mg/m ² in two divided doses	Gastrointestinal symptoms, pancreatitis, hepatitis, lipid abnormalities	—
Enfuvirtide (Fusion inhibitor)	Hepatic	Subcutaneous injection	>6 years age: 4 mg/kg in two divided doses	Local site reactions, immune-mediated reactions, hypersensitivity	—

Abbreviations: NRTI, nucleoside reverse transcriptase inhibitors; NNRTI, non-nucleoside reverse transcriptase inhibitors; PI, protease inhibitor.

vaccine, pneumococcal, varicella and hepatitis A vaccine are also recommended. However, immunizations may not always offer adequate protection in HIV-infected children.

Nutrition

Early nutritional intervention is important due to interrelation between nutrition, growth and HIV infection. Nutritional assessment and growth monitoring should be done in infants (monthly)

and children (3 monthly). Energy intake of asymptomatic HIV-infected children should be increased by 10% of recommended dietary allowance (RDA) and that of symptomatic children by 20–30% of RDA due to increased energy expenditure. In severe malnutrition, energy intake should be increased by 50–100% of RDA. Counseling should include micro- or macronutrient deficiency, selection of locally available good foods, vitamin A supplementation and information regarding food and water hygiene.

Table 9 The indications for starting antiretroviral therapy (ART) and first-line regimen in children

Population	Indication to start ART	Recommended ART
Infants < 12 months of age	Initiate in all HIV infected irrespective of CD4 count or WHO clinical staging. (all children < 5 years of age) Start as priority in HIV infected 1–2 years old or with severe/advanced HIV disease (WHO clinical stage 3 or 4) or CD4 cell count ≤ 750 cells/mm ³ or < 25% whichever lower. Any child < 18 months if presumptive clinical diagnosis of HIV.	Regardless of NNRTI exposure: LPV/r based regimen + 2 NRTI [ABC+ 3TC OR AZT+ 3TC] If LPV/r not feasible: NVP based regimen Where viral load monitoring is available, consideration can be given to substituting LPV/r with an NNRTI after virological suppression is sustained. If child on TB therapy; ABC + 3TC + AZT and replace with initial therapy once TB treatment over.
Between 12 and 24 months		Same as above
Between 24 months and < 5 years of age		24 months to < 3 years: Same as above
Children > 5 years of age	CD4 count ≤ 500 cells/mm ³ (irrespective of WHO staging) OR WHO clinical stages 3 and 4 (As priority in all children with severe/advanced HIV disease (WHO clinical stage 3 or 4) or CD4 cell count < 350 cells/mm ³) OR Active TB disease	> 3 years: EFV (or NVP alternative) + 2NRTIs 3–10 years old (< 35 kg): EFV (or NVP) + ABC+3TC EFV (or NVP) + AZT or TDF + 3TC (or FTC)
Adolescents (10–19 years old)	Same as above To start ART regardless of CD4 count or WHO staging if: Active TB disease, HBV coinfection with severe chronic liver disease	10–19 years old (>35 kg): EFV (or NVP) + TDF + 3TC (or FTC) EFV (or NVP) + AZT + 3TC EFV (or NVP) + ABC + 3TC
Children with TB	Start as above	< 3 years of age: NVP + 2 NRTIs OR 3 NRTIs [AZT or d4T+(3TC+ABC)] triple nucleoside regime ≥ 3 years: EFV + 2 NRTIs (switch back to standard first line regimen of 2NRTI + NVP after 2 weeks of completing rifampicin based ART) OR 3 NRTIs NVP + 2 NRTIs (avoid AZT)
Children with anemia	ART should be initiated regardless of WHO clinical stage or CD4 cell count in adolescents with HIV and active TB	
Adolescents > 12 years with hepatitis B	ART should be initiated regardless of WHO clinical stage or CD4 cell count in adolescents coinfectd with HBV with evidence of severe chronic liver disease	Tenofovir disoproxil fumarate (TDF) + emtricitabine (FTC) or 3TC + NNRTI

Abbreviations: AZT/ZDV, zidovudine; NFV, nelfinavir; RTV, ritonavir; ABC, abacavir; ddI, didanosine; FTC, emtricitabine; 3TC, lamivudine; NRTI, nucleotide reverse-transcriptase inhibitors; d4T, stavudine; TDF, tenofovir; NNRTI, non-nucleoside reverse-transcriptase inhibitors; EFV, efavirenz; ETV, etravirine; NVP, nevirapine; PIs, proteases inhibitors; ATV/r, atazanavir + ritonavir; DRV, darunavir; LPV/r, lopinavir/ritonavir; RAL, raltegravir.

Supportive Treatment

Counseling about the importance of good hand washing, avoiding raw or undercooked food (prevent *Salmonella* infection), avoiding drinking or swimming in lake or river water or being in contact with young farm animals (to prevent *Cryptosporidium* infection), and the risk of playing with pets (to prevent toxoplasma from cats) is essential. Simple interventions like good general hygiene, dental care, adequate nutrition (including nasogastric and parenteral nutrition if required), balanced diet, timely immunizations, vitamin A supplementation, plotting weight and height on growth charts, provision of safe and stimulating environment, developmental evaluation and interventions like occupation therapy or speech therapy can help a child with HIV to be free of infections and grow well.

HIV in Adolescents

Special considerations should be given to developmental or growth delay often associated with delayed puberty. Modifications in ART

should be specific to adolescents. In case of Tanner stages I, II or III Pediatric ARV schedule is recommended while in Tanner stages IV or V—adult schedule is recommended. One must observe caution in adolescent girls while use of EFV (those at risk of pregnancy) and NVP (CD4 counts between 250 cells/mm³ and 300 cells/mm³ due to risk of rash or hepatic toxicity). Besides this, the issues pertaining to disclosure of HIV status and long-term adherence to ART should also be addressed.

PREVENTION

Use of antiretroviral (ARV) drugs in pregnancy and breastfeeding is recommended for the mother's health and to prevent infection in the exposed baby. It may also help reduce sexual transmission. In order to accelerate the global scaling up of ART and prevention of mother to child transmission (PMTCT) in resource poor settings, ensuring global access to ART by all pregnant women and attaining global goals of eliminating new pediatric infections (and keeping mothers alive), the recommendations by WHO have been

Table 10 World Health Organization (WHO) guidelines for prevention of perinatal transmission of human immunodeficiency virus (HIV)

<i>Prevention of perinatal transmission (WHO 2013 recommendations)</i>		
Based on National PMTCT options	Treatment in mother Triple ARVs fixed-dose combination of TDF + 3TC (or FTC) + EFV (including 1st trimester of pregnancy and women of child-bearing age)	Treatment in child <i>Begin at birth or when HIV exposure recognized postpartum</i>
<i>Option B:</i> Use of lifelong ART in all HIV infected pregnant and breastfeeding women	To start ART and continue even after delivery and cessation of breastfeeding	<i>If breastfeeding:</i> 6 weeks of infant prophylaxis with once daily NVP.
<i>Option B+:</i> Use of lifelong ART in only HIV infected pregnant and breastfeeding women. <i>Eligible</i> (CD4 count below 500 cells/mm ³ or clinical stage 3 or 4 disease at the time of ART initiation or in accordance with national guidelines. Assess for second line if clinical or laboratory indication of treatment failure during above period.	<i>Eligible for treatment:</i> Start ART and continue after delivery and cessation of breastfeeding <i>Not eligible for treatment:</i> Start ART and stop after delivery (if replacement feeding) and cessation of breastfeeding (1 week after breastfeeding ends). If replacement feeding stop ART after delivery.	<i>If replacement feeding:</i> They should be given four to six weeks of infant prophylaxis with once daily NVP (or twice-daily AZT).

Abbreviations: ARV, antiretrovirals; TDF, tenofovir; 3TC, lamivudine; FTC, emtricitabine; EFV, efavirenz; ART, antiretroviral therapy; NVP, Nevirapine; AZT, zidovudine; PMTCT, preventing mother-to-child transmission.

simplified and standardized into guidelines (2013) suggesting options B or B+ based on national policies and recommendations (Table 10).

HIV and Breastfeeding (WHO Recommendations)

WHO aims to increase the HIV-free survival of infants exposed to HIV through its recommendations on HIV and infant feeding. This necessitates a balance between the risk of HIV transmission through breastfeeding as compared to risk of malnutrition and increased infections due to unsafe feeding practices. Based on national or sub-national recommendations, WHO 2010 guidelines suggest to counsel and support mothers to either breastfeed with antiretroviral (ARV) intervention or avoid breastfeeding completely to prevent HIV transmission postpartum. In countries recommending breastfeeding with ARV drugs, HIV infected mothers should exclusively breastfeed for first 6 months, then continue breastfeeding for first 12 months of life and stop only when a nutritionally adequate and safe diet without breastmilk can be ensured. Mortality due to pneumonia, diarrhea and malnutrition can be minimized by breastfeeding for first 12 months, while presence of ARV drugs reduces risk of HIV transmission to the infants. It is necessary to consider the socioeconomic and cultural context of the population, availability and quality of health services, local epidemiology and main causes of infant and child mortality before making the choice of type of feeding. HIV-infected mothers should be provided with lifelong ART or ARV prophylaxis to reduce the transmission to the child. When ARV drugs are unavailable, breastfeeding may provide infants a greater chance of survival and mothers should be counseled to exclusively breastfeed for first 6 months of life and continue breastfeeding thereafter (unless environmental and social circumstances are safe and supportive of replacement feeding). The mothers who decide to stop breastfeeding should do so gradually over a period of 1 month. The mothers or infants receiving ARV prophylaxis should continue the ARV drugs for 1 week after fully stopping the breastfeed. In such cases, infants must be provided with safe and appropriate replacement feeds. For replacement feeding, it is necessary to ensure adequate sanitary facilities, safe water supply, sufficient replacement supply (to ensure normal growth and development), adequate hygiene, family support and access to comprehensive healthcare.

Other measures to reduce transmission of HIV from mother to child are as follows:

Pregnant Women with HIV

Early identification of mothers with HIV should be done to provide ART drugs to both mother and newborn baby. One must ensure recommended antenatal visits and pregnancy care, additional screening for sexually transmitted infections, nutritional support and counseling regarding infant feeding and family planning.

Labor and Delivery

If HIV status unknown in women in labor, rapid HIV testing should be done during labor or immediate postpartum to provide ART to both mother and baby as soon as possible if tested positive. There should be facility based delivery by trained skilled birth attendants and unnecessary instrumentation or premature rupture of membranes should be avoided. Universal precautions should be carried by health workers as a usual norm. The baby's mouth and nostrils should be wiped as soon as head is delivered, infant should be handled with gloves till all maternal secretions and blood are wiped off and cord should be clamped (without milking) soon after birth.

Postdelivery

Provision of follow-up, linkages to treatment and postpartum care should be ensured. Child should be provided with initial care during first immunization visit (4–6 weeks of age), including reinforcing safe feeding measures, early infant diagnosis and ARV coverage while mother should be provided with postpartum check-up, family planning advice and review of ARV coverage and adherence support.

The Indian Government set-up the National AIDS Control Program (NACP I) and the National AIDS Control Organization (NACO) in 1992. The State AIDS Control Societies (SACS) were set up in 25 societies and 7 union territories. As the focus gradually shifted to decentralization, bringing behavioral changes and involving the non-governmental organizations (NGOs) and people living with HIV, subsequent phases were launched—NACP II in 1999 and NACP III in 2007. The Government is designing the strategy for NACP IV for period of 2012–2017, its main objectives being reduction of new infections, providing comprehensive care

and support to all people living with HIV and treatment facilities for all those requiring it. The main strategies are intensification and consolidation of preventive services, increased access and promotion of comprehensive care, support and treatment, expanding information education communication (IEC) services, building capacities at national, state, district and facility levels and strengthening strategic information management systems.

IN A NUTSHELL

1. Initially a disease of the so called *high-risk population*, HIV/AIDS has gradually and eventually penetrated upto all sections of the society.
2. With better access to antiretroviral therapy (ART), better drugs to treat opportunistic infections (OIs), the (HIV) disease has now been converted to a chronic disorder with longer survival and newer complications.
3. HIV is a multiorgan disease with varied manifestations in children due to their immature and developing immunity, allowing dissemination amongst all organ systems.
4. Clinical presentation are different in developing world where conditions like measles, tuberculosis, varicella, acute/persistent/recurrent diarrhea, etc. exist and contribute to the morbidity and mortality.
5. Failure to thrive (50–70%), hepatosplenomegaly (40–70%), anemia (40–50%), fever (30–60%), lymphadenopathy (40%), coinfection with TB (30–50%), diarrhea (20–30%), candidiasis (20%) and CNS symptoms (5–15%) are common presenting symptoms in children.
6. Children with HIV are increasingly susceptible to opportunistic infections (OIs), most common amongst which are *Pneumocystis carinii* (*jiroveci*) *pneumonia* (PCP), tuberculosis, recurrent bacterial infections, candidiasis, etc.
7. The diagnosis is by virological or serological methods. Presumptive diagnosis can also be made by certain clinical criteria in children less than 18 months where virological methods are unavailable.
8. Success of ART depends on appropriate drug selection, adherence, monitoring on ART, regular follow-up, knowledge of toxicities and drug interactions, diagnosing treatment failure early and appropriate change of ART.
9. Use of antiretroviral (ARV) drugs in pregnancy and breastfeeding is recommended for the mother's health and to prevent infection in the exposed baby.
10. Improved survival of infants exposed to HIV is aimed for through national or sub-national recommendations on HIV and infant feeding.

PROGNOSIS

The prognosis in HIV-infected children depends on availability and access to good health-care and medications (including ART). In the developed countries, progression of the HIV disease and the consequent mortality has decreased with an improved quality of life. A high viral load (>100,000 copies/mL) or CD4 lymphocyte percentage of below 15% is associated with higher mortality and morbidity. In developing countries, clinical staging system can

be effectively used to predict progression of the disease. Patients with lymphadenopathy, hepatosplenomegaly, parotitis and LIP have a comparatively better outcome. Those with OIs (PCP or MAC), severe wasting syndrome or encephalopathy have a poorer prognosis. Also, manifestations like persistent fever, serious bacterial infections (meningitis, pneumonia or sepsis), hepatitis and persistent anemia (<8.0 g/dL) with or without thrombocytopenia (<100,000/mm³) predict a poorer prognosis.

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Section 32 PARASITIC INFECTIONS AND INFESTATIONS

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Chapter 32.1

Epidemiology of Parasitic Infections

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BURDEN OF PARASITIC INFECTIONS

Parasitic infestations are widely prevalent in many developing countries, especially in the tropical and subtropical regions. These infections exert a significant effect on quality of life; and economic deprivation accrued through loss of human work hours. In an urban setting, parasitic infections in children result from ingestion of contaminated food and water or close association with their pets.

Epidemiology of parasitic infections is quite complex because of the involvement of various animals in their transmission cycle and a host of inter-related factors like environmental changes, human settlement, human behavior, food habits, population variation in animals, vectors and their densities, climate, etc., which influence the prevalence of the disease. Therefore, designing preventive and control measures is also not so simple.

Factors Influencing Prevalence

Behavioral Patterns

Human behavioral patterns including the habits, customs, traditions and socioeconomic practices are closely related to the risk of acquiring parasitic infections. Trekking, tourism, hunting, riding, mountaineering, fishing, other recreational activities and travel have increased this risk; also religious and sociocultural practices influence the prevalence of taeniasis in the community.

Food Habits

Food, food products and food habits have a role in the transmission of parasitic infections. Food-borne parasitic infections may be:

- *Directly transmissible* to humans by consuming food in which the infective stages of the parasite are naturally present, as in *Taenia*, *Trichinella*, fish-borne trematodes, *Diphyllobothrium*, *Gnathostoma*, *Angiostrongylus*, *Capillaria*, *Toxoplasma*, and *Linguatula*, or
- *Indirectly transmissible* to humans by food contaminated with infective stages of parasites derived from the environment, as with *Dracunculus*, *Echinococcus*, *Trichostrongylus*, *Trichuris*, *Fasciola*, *Ascaris*, *Toxocara*, *Toxoplasma*, *Giardia*, and *Entamoeba*, etc.

Consumption of uncooked or inadequately cooked fish and crustaceans may result in the transmission of *Diphyllobothrium latum*, *Clonorchis sinensis*, *Paragonimus westermani* and *Metagonimus*. Hydatid disease, taeniasis, toxoplasmosis and trichinosis are common parasitic infections transmitted to man through consumption of inadequately cooked meat or contamination of meat after cooking. Modern abattoir facility, stringent inspection at all stages of production, processing,

marketing, and health education are important in the control of meat-borne parasitic zoonoses.

Occupation, Migration and Settlement

Agricultural workers are more prone to vector-borne diseases and helminthiasis. Fishermen, cooks, abattoir workers are at higher risk of food-borne parasitic infections. Migration of human populations contributes significantly to the introduction of parasitic infections to new areas. Malaria, dracunculiasis, filariasis and hookworm infestations were introduced into the western world from Africa. Travel and migration may be responsible for spread of diseases to nonendemic areas; an example is *airport malaria* whereby infected mosquitoes can reach nonendemic areas. Household pets such as dogs, cats and other domestic animals may transmit toxoplasmosis and echinococcosis to their owners. National parks and wildlife sanctuaries also provide optimum conditions for perpetuation and transmission of different parasites.

Environmental Pollution

Climate, food supplies and hydrodynamic changes influence the perpetuation and dissemination of parasitic zoonosis. Fecal contamination of soil, water supply and vegetables is an important mode of environmental pollution that significantly influences the prevalence of parasitic disease, especially geohelminths, in both rural and urban areas. Stagnation of water and inadequate drainage increase breeding sites of the insect vectors of many parasitic infections.

Human activities such as irrigation schemes, construction of dams and other water reservoir development projects, establishment of new settlements, agricultural and industrial activities, affect the ecosystem in a way that makes it conducive for spread of parasitic infections.

HOST-PARASITE RELATIONSHIP

Parasites live in, on, or at the expense of the living organism. *Obligatory parasites* cannot complete their life-cycle without passing through a host. A few parasites, e.g., *Strongyloides stercoralis* are capable of living and completing their development even without a host. These are called *facultative parasites*.

Definitive Host

Man is the definitive host for many helminths. The adult and the sexual forms of parasites live in the body of the man, e.g., *Ascaris lumbricoides*, *Enterobius vermicularis*, *Ancylostoma duodenale* and *Necator americanus*. The parasites, however, may be capable of completing their life-cycle in other animals beside man. These animals serve as reservoirs of infection.

Intermediate Host

The intermediate host harbors the larval, immature or asexual forms of the parasite. Man is the intermediate host as well as the definitive host for some helminths, e.g., *Taenia solium* and *T. saginata*. Cattle are the intermediate hosts for *T. saginata* and pigs for *T. solium*, man for *Echinococcus* and fish for *Diphyllobothrium latum*.

At times, further development of the larval forms in the intermediate host is arrested; no further multiplication occurs and the parasite gets encysted, e.g., in cysticercosis caused by *T. solium*.

Infective Forms

- Eggs *Ascaris lumbricoides* and *Enterobius vermicularis*. In case of *Taenia solium*, and *T. saginata* the eggs develop into larvae in the intestines. The larvae pierce the gut wall and are encysted in various tissues.
- Larvae *Ancylostoma duodenale*, *Necator americanus* and *Strongyloides stercoralis*; cyclops, *Dracunculus medinensis*, cercaria, fasciolopsiasis, schistosomiasis.
- Cysts of larvae in cases of *Taenia solium* and *T. saginata* remain embedded in the flesh of pigs or cattle and may be eaten by man, developing into adult worms in the intestine.

SOURCES

Parasitic infections may be acquired from human, animal or inanimate sources.

Human Source

Infected individuals having amebiasis, pinworms and dwarf tapeworm infections are responsible for direct transmission of the infection to other human hosts.

Animal Source

Herbivores are an important source of infection to man. *T. saginata* is acquired by eating beef. Dogs are responsible for the transmission of hydatid disease. Blood sucking arthropods transmit malaria, leishmaniasis, trypanosoma and filariasis. Certain animals like sheep, cattle, pigs, etc., may serve as reservoirs of parasitic infections.

Inanimate Sources

Water may get contaminated with cysts of intestinal flagellates, protozoans, and cercariae of blood flukes. Soil may harbor eggs of roundworm, hookworm, *Trichuris* and *Strongyloides*. *Enterobius* can be transmitted via infected bed clothes, etc.

TRANSMISSION

Ingestion and inoculation are the two primary routes of transmission of infection to man. Certain other and less frequent routes of transmission are congenital, venereal and through inhalation.

Ingestion

Ingestion of food or drinks contaminated with cyst or ova of intestinal parasites, free infective larvae of *Trichostrongylus* spp. and the mature larval stages of intestinal flukes, lung flukes, *Trichinella spiralis*, *Diphyllobothrium latum*, *Taenia saginata* and *Taenia solium* may transmit the infection. *Ascaris lumbricoides*, *Enterobius*, *Hymenolepis nana*, *T. solium* infections may occur by eating food contaminated with the eggs. *Dracunculus medinensis* infection occurs by taking water containing the cyclops, the intermediate host.

Inoculation

Plasmodium, *Leishmania*, *Trypanosoma*, *Babesia*, and filarial parasite are transmitted by the bite of arthropod vectors. The infective forms of hookworms, schistosome and *Strongyloides stercoralis* pierce intact skin to invade the human body.

Other Routes

Toxoplasma gondii can cross the placenta causing congenital infection of the fetus; less frequently, malaria may be transmitted transplacentally. *Trichomonas vaginalis*, *Entamoeba histolytica*

and *Giardia lamblia* may be transmitted by vaginal and anal sexual contact respectively. Eggs of pinworm can occasionally be air-borne and transmitted by inhalation. *Strongyloides* and *Ancylostoma* may be transmitted occasionally by the transmammary route. *Plasmodium*, *Trypanosoma* and some other parasites may be transmitted by blood transfusion.

PATHOGENESIS

Parasitic infections invoke a variety of host reactions which depend on several factors: number of invading parasites, the growth, development and multiplication of parasite inside the host, and the sites of attachment of parasites. The reactions of the host to infection by the parasite may range from subclinical latent infection to the development of an overt clinical illness which may be mild, severe or fulminant. The various methods by which parasites may cause damage to the host are as follows:

Invasion

Hookworm, *Strongyloides*, *Enterobius* or *Taenia* attach to the intestinal wall causing traumatic damage to the intestinal villi. Hookworm attachment and their migration to another site may cause bleeding from the initial site. The usual losses are 0.04–0.15 mL of blood per worm per day resulting in anemia. Roundworms may also deprive the host of the nutrients.

Mechanical Damage

Roundworms or tapeworms may cause intestinal obstruction. They may also cause jaundice by blocking the ampulla of Vater; hydatid cysts may form large masses in the liver, lungs or other viscera; cysticerci may lodge in vital parts of the body including brain. In schistosomiasis, deposition of eggs inside the urinary bladder or intestinal mucosa leads to hemorrhages in the lumen of these organs.

Direct Trauma

Several helminthic larvae cause traumatic damage in lungs during their migration. *Paragonimus* infects lungs leading to its direct trauma. Identical damage may occur in the cerebral, renal or retinal capillaries and can be serious and often fatal.

Allergic Manifestations

Certain parasites may release their metabolic by-products into circulation which may behave like foreign antigens and produce a variety of allergic manifestations in the sensitized host. In dracunculiasis, migration of the gravid female to surface of the skin produces a local blister and an allergic reaction due to the release of the excretory or metabolic by-products of the parasite. Dracunculiasis and trichinellosis may also result in anaphylactic reactions, urticaria and eosinophilia. Hydatid cyst in the body cavity may rupture resulting in anaphylactic manifestations; fluid from *Ascaris* can also produce anaphylactic reactions. Cerebral cysticerci may die following chemotherapy leading to intense allergic reactions, brain edema and death. *Toxocara canis* may cause severe tissue damage due to hypersensitivity reaction.

Lysis and Necrosis

Entamoeba histolytica secretes several lytic enzymes. These include proteases, collagenases and perforins, etc., which digest intestinal tissue and also aid in the penetration and perforation of the large intestine. The parasites obtain their nourishment from lysed cells and utilize this energy for their growth and multiplication.

Inflammation

An acute inflammatory reaction occurs in various muscular tissues, around the larvae of *Trichinella*. Trichinellosis and strongyloidiasis

are invariably associated with eosinophilia. *E. histolytica* produces an intense tissue reaction in the large intestine of the host resulting in the formation of amebic granuloma. The eggs of the blood flukes deposited inside the vesical and intestinal mucosa incite local inflammatory reactions ending up in the evolution of granulomas that may undergo carcinomatous changes in prolonged and chronic infections.

Blood Loss

Destruction of red blood cells in malaria, mechanical loss of blood in hookworm infection or extensive invasion of the colon in intestinal amebiasis, frequently stimulates increased erythropoiesis in the body.

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Chapter 32.2

Malaria

Ritabrata Kundu

Malaria is a major health problem in India. Though the total number of malaria cases has decreased from near 2 million per year in the beginning of this millennium to 1.5 million in last few years but the percentage of falciparum malaria contributing to the burden is on rise. At present falciparum malaria constitute 50% of total malaria cases in India. Malaria now is a dual species infection with equal contribution by both *Plasmodium vivax* and *Plasmodium falciparum*.

ETIOLOGY

Four species of the genus *Plasmodium* namely *P. vivax*, *P. falciparum*, *P. ovale* and *P. malariae* are mainly responsible for malaria. Of these, first two accounts for nearly all the cases of malaria in India. Few cases of *P. ovale* are reported from Orissa. The disease is not seen 2,000 m above mean sea level and thrives in high humidity with ambient temperature between 20°C and 30°C. The disease is transmitted by female anopheline mosquito with *Anopheles stephensi* and *Anopheles culicifacies* as the main vectors in urban and rural areas, respectively.

EPIDEMIOLOGY

The disease initially restricted to rural areas of eastern and northeastern states of India has also spread to the central and arid western parts of the country. Thereafter due to unplanned expansion of the megacities and town, urban malaria starting as a minor problem, has expanded to contribute about 10% of total malaria cases. The magnitude of the problem was further enhanced by *P. falciparum* developing resistance to first-line drug chloroquine (CQ). Despite a few stray reports of CQ resistant *P. vivax*, the drug at present still retains its efficacy against vivax malaria.

CQ resistant falciparum, first detected in northeastern part of India, has spread across. At present about 80 districts of 21 states of India report CQ resistant falciparum malaria. Resistance to second-line antimalarial drugs sulfadoxine-pyrimethamine (SP) has been reported from seven northeastern states, Orissa and few districts of West Bengal. Factors responsible for resistance include unplanned development, deforestation, population movement, infrastructure deficiency, and haphazard use of antimalarial drugs, and presumptive treatment based on clinical signs alone.

TRANSMISSION

Malaria in India has unstable transmission dynamics. The disease is seasonal increasing during and following monsoon rains. Hence, the population has little or no immunity toward malaria and all age groups are at risk of developing the disease. In some foci where the transmission is intense round the year particularly forested areas it is the child who bears the brunt of the disease. Children have lost the little immunity they acquired from their mother after infancy and have not yet developed immunity of their own.

PATHOGENESIS

Malaria is transmitted to human by the bite of female anopheline mosquito. Sporozoites from the mosquito enter the circulation and are taken up by the hepatocytes to produce merozoites. With rupture of the liver cells merozoites are liberated in the blood

stream. In case of vivax malaria some sporozoites in liver cells instead of multiplying to merozoites assume an inert stage known as hypnozoites. These hypnozoites may become active after weeks or months to cause relapse in vivax malaria. Hypnozoites are not produced in falciparum malaria hence there is no relapse. Merozoites from ruptured liver cells in blood enter the red blood cells (RBCs) with vivax showing preference for young cells and falciparum without any preference. Hence, more red cells are invaded in falciparum malaria as compared to vivax. During this phase of erythrocytic cycle also known as erythrocytic schizogony, malaria parasite passes through the stages of early ring form, trophozoite, schizont and merozoite. Ultimately the parasite occupies the entire red cell which becomes rigid and deformed with full of merozoites. Swollen red cell ruptures with release of multiple merozoites which again invades fresh red cells to start a new asexual cycle.

In *P. vivax* malaria the cycle of erythrocyte schizogony is completed in the peripheral circulation. Schizogony in falciparum malaria occurs in the capillaries of the internal organs like spleen, liver, brain, etc., with only the early ring forms usually seen in the peripheral blood. RBC containing the mature forms of falciparum parasite, i.e., beyond early ring form renders the red cells sticky. This causes two important problems in falciparum malaria parasitized RBC adhere to microvascular endothelium (*cytoadherence*) and also they adhere to uninfected erythrocyte (*rosetting*). The net result is impedance in forward flow of blood in venules and capillaries of vital organs leading to microcirculatory obstruction. When this obstruction involves the capillaries of brain it results in cerebral malaria and similarly in gut leads to algid malaria.

After a series of asexual cycles, some merozoites instead of developing into trophozoites and schizonts gives rise to male and female gametocytes, which are capable of sexual functions outside the human host. Gametocytes do not cause any fever in human host but are produced for propagation of the species. Female anopheles mosquito during its blood meal from an infected person ingests both male and female gametocytes. These gametocytes undergo series of developmental process in the mosquito with ultimate release of sporozoites, which concentrate in the salivary glands of the mosquito. Following the bite of an infected anopheline mosquito the sporozoites are introduced in the human to continue the cycle.

Besides obstructing the microcirculation of vital organs thereby interfering with tissue metabolism malaria causes destruction of RBC with liberation of parasites and degraded erythrocytes along with host reaction. Following malaria there is humoral response to infection which is not enough to contain the infection. Cell-mediated immunity against malaria is also ineffective as blood stage parasites in RBC do not express human leukocyte antigen (HLA) antigens.

Recrudescence of Malaria

Often due to incomplete treatment some erythrocytic form of parasite survives in human host and only with time it multiplies and produces recurrence of symptoms of malaria. This is especially seen in case of *P. falciparum* malaria and is known as recrudescence. It can be seen as long as 10 weeks following treatment.

CLINICAL DISEASE

Malaria in India, unlike high transmission areas of Africa, fluctuates greatly over seasons and years. This seasonal variation hinders the population from acquiring lasting immunity against malaria. Hence all age groups suffer from acute malaria with chances of progression to severe malaria particularly in cases of *P. falciparum* infection.

It is very important to distinguish uncomplicated and complicated or severe malaria as the later needs highest level of patient care for favorable outcome. If treatment is delayed or ineffective in early uncomplicated stage of *P. falciparum* malaria, the parasitic mass will rapidly increase to produce organ dysfunction resulting in severe malaria.

Initial symptoms of malaria are nonspecific and may resemble any viral fevers like influenza. Both the species cause muscle ache, headache, lethargy and vague abdominal pain. *P. vivax* malaria may cause well defined fever paroxysm with chills and rigor. *P. falciparum* malaria on the other hand may cause erratic fever and it may not regularize to any definitive paroxysm. The classical stages with cold, hot and sweating features may not be seen. Children may be extremely lethargic, anorectic and at times irritable. As the disease continues, spleen and liver enlarge with developing anemia. Mild abdominal discomfort is common in malaria with occasional constipation or diarrhea. Respiratory rate may increase due to dehydration, acidosis and anemia. These symptoms and signs are nonspecific resembling many common infections in children. Thus symptomatic diagnosis of malaria invariably leads to overdiagnosis.

Complicated or Severe Malaria

Complicated or severe malaria is defined as symptomatic malaria with signs of severity or evidence of vital organ dysfunction. Severe malaria due to *P. vivax* is rare. Occasional severe manifestation in vivax malaria may be due to splenic rupture either traumatic or spontaneous. Other manifestations include severe anemia, hypersplenism and at times cerebral malaria. Most of the complicated malaria are due to *P. falciparum* and early recognition is of utmost importance. Any of the following clinical or laboratory features in presence of asexual parasitemia are suggestive of complicated or severe malaria:

- **Cerebral malaria** Unrousable coma not attributable to any other cause in a patient with falciparum malaria.
- **Severe anemia** Anemia is a common finding in severe malaria particularly in children and pregnant women. Hemoglobin in often below 5 g/dL and hematocrit below 15%.
- **Hypoglycemia** It is defined as whole blood glucose concentration less than 40 mg/dL (2.2 mmol/L).
- **Respiratory distress (acidosis)** It is defined as arterial or capillary pH below 7.35 or plasma bicarbonate concentration below 15 mmol/L.
- **Circulatory collapse or shock (algid malaria)** Defined as systolic blood pressure less than 50 mm Hg in children (1–5 years) or less than 80 mm Hg in adults.
- **Pulmonary edema** It is one of the grave complications of severe malaria but fortunately less common in children.
- **Abnormal bleeding and disseminated intravascular coagulation (DIC).**
- **Renal failure** Defined as serum creatinine more than 3.0 mg/dL or urine volume less than 0.5 mL/kg/hour in children or 400 mL in 24 hours in adults despite normal hydration.
- **Hemoglobinuria** This is due to acute intravascular hemolysis accompanied by hemoglobinuria.
- **Jaundice** Defined as serum bilirubin more than 3 mg/dL or presence of clinical jaundice. If present with other signs of severe malaria then it is significant.
- **Hyperparasitemia** There is no agreed definition of hyperparasitemia. In high transmission area if the proportion of parasitized RBCs is 10% or more and in low transmission area the proportion is 5% more, then it is taken as hyperparasitemia.

Severe malaria in children is an emergency. Unlike adults, uncomplicated malaria progressing to severe malaria is rapid within 1 day or 2 days but resolution of coma is also rapid. Common

manifestations of severe malaria in children are cerebral malaria, severe anemia, respiratory distress with acidosis and hypoglycemia. Mortality is high in children in deep coma with acidotic breathing. Jaundice and pulmonary edema are uncommon in children and renal failure is a rare entity. Neurological sequel following cerebral malaria is more frequent in this age group as compared to adults.

DIAGNOSIS OF MALARIA

Diagnosis of malaria based on symptoms should be discouraged as it invariably leads to overdiagnosis. All cases of suspected malaria should have a parasitological diagnosis and with advent of rapid diagnostic test which does not need expertise, it is available even in the periphery. However, in complicated malaria or malaria with danger signs presumptive treatment may be started before confirmation after collecting blood for examination.

Microscopic Diagnosis

Light microscopy of well-stained thick and thin films by a skilled microscopist has remained the *gold standard* for malaria diagnosis. Thick films are nearly 10 times more sensitive for diagnosis of malaria as larger amount of blood are there in a given area as compared to thin films. Species identification is better with thin films as morphology of the parasite and RBCs are well preserved.

Timing of sample collection should be as soon as malaria is suspected. It can be collected any time irrespective of fever and not necessarily only at the height of fever. Collection should be before administration of antimalarial, which causes detection of parasites difficult due to its morphologic alteration.

Smears should be prepared soon after collection, which enables better adherence of films to the slide and cause minimal distortion of parasites and red cells. In blood collected with anticoagulants films should be prepared within 2 hours for best results. Smear should be examined with 100X oil immersion objective. A minimum of 100 fields should be examined before concluding the slide to be negative. Once negative, samples may be examined for at least 3 consecutive days where clinical suspicion of malaria persists.

Rapid Diagnostic Tests

These are immunochromatographic tests (ICT) to detect plasmodium specific antigens in blood sample. Test employs monoclonal antibodies directed against targeted parasite antigens. Targeted antigens in currently available rapid diagnostic tests (RDTs) are described below:

- **Histidine rich protein II (HRP-II)** is actively secreted by asexual stages and young gametocytes of *P. falciparum* but not by mature gametocytes.
- A metabolic enzyme **parasite lactate dehydrogenase (pLDH)** is produced by all four species of plasmodia, both asexual and sexual (gametocytes) stages provided they are viable. Monoclonal antibodies produced against this antigen are of three groups. One specific for *P. falciparum* and the second specific for *P. vivax*. The other is panspecific antibody which reacts with all the four species of plasmodia, i.e., *vivax*, *falciparum*, *ovale* and *malariae* but unable to differentiate them individually. Commercially available kits can detect *falciparum*, *vivax* and other malaria but cannot differentiate *ovale* and *malariae* malaria.
- Certain new antigens like plasmodium aldolase, an enzyme of the glycolytic pathway produced by all four species has been recently developed.

In India where falciparum and vivax malaria parasite cocirculate, typically occurring as a single species infection; a RDT which can detect both falciparum and vivax malaria and also distinguish between them is warranted. There are some

commercially available kits, which detect falciparum specific LDH and panspecific LDH. They can distinguish between falciparum from nonfalciparum malaria. Problem with these kits are two-fold: firstly they cannot distinguish falciparum malaria from mixed infection, secondly as vivax malaria is almost the only non-falciparum malaria in India so often they equate nonfalciparum malaria with vivax malaria.

The World Health Organization (WHO) has recommended for RDTs a minimum standard of 95% sensitivity with *P. falciparum* densities of 100 parasite/μL of blood and a specificity of 95%. RDTs using HRPII are generally more sensitive than RDTs detecting *P. falciparum* specific pLDH. *P. vivax* specific monoclonal antibodies have undergone limited evaluation. Unfortunately independent peer reviewed evaluation for most commercially available RDTs is not available. In general with high parasite density these tests are fairly sensitive but with low parasite load sensitivity decreases often yielding false negative results. False positive result may also develop when gametocytes are present but asexual stage parasites are eradicated by therapy.

HRPII antigen persists at detectable levels for more than 28 days even after successful therapy. Aldolase and pLDH rapidly fall to undetectable levels after initiation of effective therapy but these antigens are expressed in gametocytes which may appear after clinical infection is cleared. So none of the RDTs are useful for monitoring the response to treatment for which microcopy is the investigation of choice. However, they are usually simple without much training requirement, easy to interpret, and results are available rapidly. The stability of the kit in high environmental temperature and humidity of tropics should be taken into account.

Role of RDTs in the Diagnosis of Malaria in India

Microscopic diagnosis needs expertise and is unavailable in remote parts with poor health infrastructure. So RDTs will be useful in following situations in India:

- In remote areas with poor health infrastructure where microscopic diagnosis is not available. Also in areas where laboratory service is inadequate, of an unacceptable standard or not available at odd hours.
- In places where both RDT and microscopy are available they can complement each other. RDTs will provide screening diagnosis in suspected cases whereas microscopy reserved for resolution of doubtful cases, confirmation of negative result in RDTs with high clinical suspicion of malaria.
- Microscopy may fail to demonstrate parasite due to sequestration in capillaries of the organs whereas RDT can pickup antigen in this cases.
- According to the National drug policy of malaria (2013) all fever cases clinically suspected of malaria should be investigated for confirmation of malaria by microscopy or RDT.

RDTs permit on the spot confirmation of malaria even at the peripheral health-care system, by unskilled health worker with minimal training. This will reduce unnecessary treatment based on symptomatic diagnosis hence in turn decrease drug pressure.

Other Methods of Diagnosis

Other diagnostic methods namely microscopy using fluorochromes, molecular probes, polymerase chain reaction (PCR) and serology are available. Unfortunately they are not suitable for routine disease management and their use is currently for only research and epidemiological purpose.

MANAGEMENT OF UNCOMPLICATED MALARIA

Malaria parasite develops resistance to drugs randomly due to *de novo* genetic mutations. As nonimmune patients in India are

infected with large number of parasites, if they receive inadequate treatment are a potent source of *de novo* resistance. Here lies the importance of prescribing highly effective treatment regimen in high parasitemic patients and ensuring good adherence to prescribed drugs.

It has been noted that monotherapy for falciparum malaria invariably results in failure. Sulfadoxine-pyrimithamine introduced following CQ resistance fell rapidly to resistance in the early 1980s. Whereas mefloquine (MQ) introduced as monotherapy for falciparum malaria took only 4–5 years to report resistance. To counter the threat of resistance of falciparum to monotherapy, WHO now recommends combinations of antimalarials for the treatment of falciparum malaria.

Antimalarial Combination Therapy

Antimalarial combination therapy is the simultaneous use of two or more blood schizonticidal drugs with independent mode of action and targeting different biochemical stages in the parasite. If two drugs with different mode of action and different resistance mechanism are used in combination then the probability of developing resistance to both drugs is the product of their individual per parasite probabilities. If a mutant parasite develops *de novo* resistance during the course of infection to one drug it will be killed by the other drug. However, to reap the benefit of combination therapy the partners in the combination should be individually effective. This mutual protection will prevent or at least delay emergence of resistance to individual drug. The only disadvantage of combination therapy is increased risk of adverse effect and increased cost of therapy.

According to WHO, one of the partners in combination therapy will be artemisinin and its derivatives hence known as artemisinin-based combination therapy (ACT). The reason for choosing artemisinin is its rapid clearance of parasitemia and resolution of symptoms. They reduce the parasite number by approximately 10,000 fold (10^4) in each asexual cycle. The second important reason is its rapid elimination from the body so that the residual concentration of the drug does not provide a selective filter for resistant parasites. The other reasons are its lack of serious adverse effects, absence of significant resistance till date, and reducing gametocyte carriage due to its gametocytocidal action.

Artemisinin if combined with other rapidly eliminated antimalarials like tetracycline or clindamycin, a 7 days course of treatment is required. This long course invariably results in poor adherence. But when combined with slowly eliminated antimalarials like SP, MQ or lumefantrine, shorter courses of treatment (3 days) will be effective and also ensure adherence. In 3 days ACT regimen, artemisinin is present in the body during the two asexual parasite life cycles each lasting for 2 days. This treatment reduces the number of parasites in the body by a factor of approximately one hundred million ($10^4 \times 10^4 = 10^8$). The complete clearance of the parasites is dependent on the partner medicine being effective and persisting at parasitocidal concentration until all the infecting parasites have been killed. Thus the partner compound is to be relatively slowly eliminated.

As a result of combination therapy the artemisinin component is protected from resistance by the partner medicine provided it is efficacious and partner medicine is in turn protected by the artemisinin derivative.

The following ACTs are currently available in India:

- Artesunate (AS) + SP
- Artesunate + MQ
- Artemether + Lumefantrine

Of these, artemether-lumefantrine is available as coformulated tablets and liquid preparation. Lumefantrine is not available as

monotherapy, and it has been never used alone for the treatment of malaria. Other combinations are available separately.

Treatment Regimes for Uncomplicated Malaria

Treatment regimens are to be tailored specifically according to the resistance pattern of the region under consideration. However, in view of gradually increasing resistance it has been decided that all falciparum cases should be treated with ACT both in public or private health-care system to win the war against ongoing drug resistance. All cases of mixed infection, i.e., *P. vivax* and *P. falciparum* are to be treated as falciparum malaria along with primaquine for 14 days. Treatment regimes are to be tailored specifically according to the resistance pattern of the region under consideration (**Boxes 1 to 3**).

BOX 1 Recommended treatment of uncomplicated *P. vivax* malaria

Recommended treatment

Chloroquine 10 mg base/kg stat orally followed by 5 mg/kg at 6, 24 and 48 hours (total dose 25 mg/kg)

OR

Chloroquine 10 mg base/kg stat orally followed by 10 mg/kg at 24 hours and 5 mg/kg at 48 hours (total dose 25 mg base/kg)

Primaquine should be given in a dose of 0.25 mg/kg once daily for 14 days to prevent relapse

- Chloroquine should not be given in empty stomach and in high fever. Temperature should be brought down first. If vomiting occurs within 45 minutes of a dose of chloroquine that particular dose is to be repeated after taking care of vomiting by using antiemetic (domperidone/ondansetron).
- As primaquine can cause hemolytic anemia in children with G6PD deficiency they should be preferably screened for the same prior to starting treatment. As infants are relatively G6PD deficient it is not recommended in this age group and children with 14 days regimen should be under close supervision to detect any complication. In cases of borderline G6PD deficiency once weekly dose of primaquine 0.6–0.8 mg/kg is given for 6 weeks.

BOX 2 Recommended treatment of uncomplicated *P. falciparum* malaria in all states other than North-eastern states of India

Recommended treatment

Artesunate 4 mg/kg of body weight orally once daily for 3 days and a single administration of SP as 25 mg/kg of sulfadoxine (S) and 1.25 mg/kg of pyrimethamine (P) on day 1

OR

Artesunate as above and mefloquine 25 mg/kg of body weight in two divided doses (15 mg/kg and 10 mg/kg) on day 2 and day 3.

OR

Coformulated tablets containing 20 mg of artemether and 120 mg of lumefantrine can be used as a six dose regimen orally twice a day for 3 days. For 5–14 kg body weight 1 tablet at diagnosis, again after 8–12 hours and then twice daily on day 2 and day 3. For 15–24 kg body weight same schedule with 2 tablets. For 25–35 kg body weight and above same schedule with 3 and 4 tablets respectively.

AND

A single dose of primaquine (0.75 mg/kg) is given for gametocytocidal action.

- Currently there are insufficient safety and tolerability data on mefloquine at its recommended dosage of 25 mg/kg body weight in children. Mefloquine shares cross resistance with quinine which is still an effective drug in India. Health planners of India do not advocate use of mefloquine.
- Advantage of artemether-lumefantrine combination is that lumefantrine is not available as monotherapy and has never been used alone for the treatment of malaria. Lumefantrine absorption is enhanced by coadministration with fatty food like milk.
- Artemether-lumefantrine is not recommended in children weighing less than 5 kg.

BOX 3 Recommended treatment of uncomplicated *P. falciparum* malaria in North-eastern states of India

Recommended treatment

Coformulated tablets containing 20 mg of artemether and 120 mg of lumefantrine can be used as a six dose regimen orally twice a day for 3 days. For 5–14 kg body weight 1 tablet at diagnosis, again after 8–12 hours and then twice daily on day 2 and day 3. For 15–24 kg body weight same schedule with 2 tablets. For 25–35 kg body weight and above same schedule with 3 and 4 tablets respectively.

OR

Artesunate 4 mg/kg of body weight orally once daily for 3 days and mefloquine 25 mg/kg of body weight in two divided doses (15 mg/kg and 10 mg/kg) on day 2 and day 3.

AND

A single dose of primaquine (0.75 mg/kg) is given for gametocytocidal action.

Treatment Failure

Classification of treatment failure are based on both presence of fever or other signs of malaria along with peripheral parasitemia. Early treatment failure occurs if patients develops clinical or parasitological symptoms within first 3 days of follow-up. Late treatment failure is from day 4 to day 28 of follow-up. Treatment failure always doesn't mean resistance as poor adherence, poor drug quality and abnormal pharmacokinetic property of the patient may also be responsible. So, a proper treatment history is essential along with parasitological confirmation of failure by microscopy as RDTs (HRPII based) may remain positive for weeks following therapy. Failure within first 14 days of therapy should be treated with second-line antimalarials, which is quinine with tetracycline or doxycycline or clindamycin. Failure after 14 days of therapy which can be a new infection also may be treated with first-line ACT.

MANAGEMENT OF SEVERE MALARIA

Severe life-threatening malaria is nearly always due to *P. falciparum*. All cases with severe manifestations are to be treated in the same line of complicated malaria with injectable antimalarials irrespective of the species. High degree of suspicion of severe malaria is of utmost importance and any delay in initiation of treatment can be fatal. It should be treated as a medical emergency at highest level of medical facility available preferably in a intensive care setting. Confirmation of the diagnosis is preferable but one should not delay the treatment if it needs more than 1 hour. Further in cases of strong clinical suspicion prompt antimalarial therapy is needed even if parasite are not found in the initial blood examination. Effective therapy in children with severe malaria includes antimalarial chemotherapy, supportive management and management of complications. All these three interventions are equally important and to be taken care of simultaneously.

Antimalarial Chemotherapy of Severe and Complicated Malaria (Table 1)

Ideally, antimalarial drug should be given initially by intravenous (IV) infusion, which should be replaced by oral administration as soon as condition permits. Antimalarials should be given according to the body weight of the patient. If parenteral injection is not possible, referral is likely to be delayed and artemisinin is not available as suppository form crushed antimalarial may be given by nasogastric tube. It has the risk of causing vomiting and may produce inadequate drug levels in the blood. According to the National Antimalaria Program (NAMP), in all cases of severe malaria either IV quinine or parenteral artemisinin derivatives is to be given irrespective of CQ resistance status.

Table 1 Recommended treatment of complicated and severe malaria

Drug	Dosage
Quinine salt	<p>20 mg salt/kg (loading dose) diluted in 10 mL of isotonic fluid/kg by infusion over 4 hours. Then give a maintenance dose of 10 mg salt/kg every 8 hours, calculated from beginning of previous infusion, until the patient can swallow, then quinine tablets, 10 mg salt/kg 8 hourly to complete a 7 day course of treatment (including both parenteral and oral). Tetracycline or doxycycline or clindamycin is added to quinine as soon as the patient is able to swallow and should be continued for 7 days.</p> <p>Tetracycline (more than 8 years) or doxycycline (more than 8 years) to be given for 7 days 4 mg/kg/dose 4 times daily or 3.5 mg/kg once a day respectively. Clindamycin to be given 20 mg/kg/day in two divided doses for 7 days.</p> <p>If controlled IV infusion cannot be administered then quinine salt can be given in the same dosages by IM injection in the anterior thigh (not in buttock).</p> <p>The dose of quinine should be divided between two sites, half the dose in each anterior thigh. If possible IM quinine should be diluted in normal saline to a concentration of 60–100 mg salt/mL. (Quinine is usually available as 300 mg salt/mL). Tetracycline or doxycycline or clindamycin should be added as above.</p> <p style="text-align: center;">OR</p>
Artesunate	<p>2.4 mg/kg IV stat then at 12 and 24 hours, then once a day. Once the patients is able to swallow oral medication, complete the treatment by giving a course of</p> <ul style="list-style-type: none"> • Artemether plus lumefantrine in North-eastern states as shown in Box 3. • Artesunate plus sulfadoxine-pyrimethamine in all states other than North-eastern states of India as shown in Box 2. <p style="text-align: center;">OR</p>
Artemether	<p>3.2 mg/kg (loading dose) IM, followed by 1.6 mg/kg daily. Once the patients is able to swallow oral medication, complete the treatment by giving a course of</p> <ul style="list-style-type: none"> • Artemether plus lumefantrine in North-eastern states as shown in Box 3. • Artesunate plus sulfadoxine-pyrimethamine in all states other than North-eastern states of India as shown in Box 2.

- Parenteral treatment in severe malaria should be continued at least for 24 hours irrespective of patients ability to tolerate oral medication earlier than 24 hours.
- Loading dose of quinine should not be used if the patient has received quinine, quinidine or mefloquine within the preceding 12 hours. Alternatively loading dose can be administered as 7 mg salt/kg by IV infusion pump over 30 minutes, followed immediately by 10 mg salt/kg diluted in 10 mL isotonic fluid/kg by IV infusion over 4 hours.
- Quinine should not be given by bolus or push injection. Infusion rate should not exceed 5 mg salt/kg/hour.
- If there is no clinical improvement after 48 hours of parenteral therapy the maintenance dose of quinine should be reduced by one-third to one-half, i.e., 5–7 mg salt/kg.
- Quinine should not be given subcutaneously as this may cause skin necrosis.
- Artesunate, 60 mg per ampoule is dissolved in 0.6 mL of 5% sodium bicarbonate diluted to 3–5 mL with 5% dextrose and given immediately by IV bolus (push injection).
- Artemether is dispensed in 1 mL ampoule containing 80 mg of artemether in peanut oil.
- Mefloquine should be avoided in cerebral malaria due to neuropsychiatric complications associated with it.

Choice of Therapy

Artemisinins are the most rapidly acting of all known antimalarial drugs, they often produce a 10,000-fold reduction of parasites per asexual cycle. They have the broadest time window of antimalarial effects from ring forms to early schizonts. Thus they can stop parasite maturation, particularly from the less pathogenic circulating ring stages to the more pathogenic cytoadherent stages. Artemisinin also has an excellent safety profile and the cost of therapy as compared to quinine is almost similar. There are no reports of resistance to artemisinin at present but declining sensitivity to quinine has been reported from some Southeast Asian countries like Thailand. Randomized trials comparing artesunate and quinine from Southeast Asia show clear evidence of benefit with artesunate. However, artemisinin should be used when rate controlled IV infusion of quinine is not possible, patients have contraindications to quinine use and evidence of inadequate response or resistance to quinine noted. Simultaneous use of quinine and artemisinin is not indicated as it may be harmful and there is no added advantage. In limited studies available artesunate has been found to be better than artemether.

MANAGEMENT OF COMPLICATED AND SEVERE MALARIA

Of the various complications of falciparum malaria the common and important ones in children are as follows:

- Cerebral malaria
- Severe anemia
- Respiratory distress (acidosis)
- Hypoglycemia.

Cerebral Malaria

It may present like any other infection with fever followed by inability to eat or drink. The progression to coma or convulsion is very rapid within 1 or 2 days. Convulsions may be very subtle with nystagmus, salivation or twitching of an isolated part of the body. Other treatable causes of coma (e.g., bacterial meningitis, hypoglycemia) should be excluded. Good nursing care, management of convulsions with diazepam/midazolam and avoidance of harmful ancillary treatment like corticosteroids, mannitol, adrenaline and phenobarbitone is needed.

Severe Anemia

Children with hyperparasitemia due to acute destruction of red cells or malaria in children with already existing nutritional anemia may develop severe anemia. Packed red cell transfusion should be given slowly and cautiously when packed cell volume (PCV) is 12% or less, or hemoglobin is below 4 g%. Transfusion should also be considered in patients with less severe anemia in the presence of respiratory distress (acidosis), impaired consciousness or hyperparasitemia.

Lactic Acidosis

Deep breathing with indrawing of lower chest wall without any localizing chest signs suggest lactic acidosis. Commonly seen in patients with cerebral malaria, anemia or dehydration. Judicious fluid therapy to correct hypovolemia, treatment of anemia and

prevention of seizures are needed. Monitoring acid base status, blood glucose and urea and electrolyte level are also important.

Hypoglycemia

Common in children less than 3 years especially with hyperparasitemia or with convulsion and particularly in patients treated with quinine. As manifestations are similar to those of cerebral malaria so it can be easily overlooked unless looked for carefully hence monitor blood sugar every 4–6 hourly. If facilities to monitor blood glucose are not available assume hypoglycemia in symptomatic patient and treat accordingly. Correct hypoglycemia with IV dextrose and it should be followed by slow infusion of 5% dextrose containing fluid to prevent recurrence.

Hyperpyrexia

High fever is common in children and may lead to convulsion and altered consciousness. Tepid sponging, fanning and paracetamol 15 mg/kg should be given.

PREVENTION OF MALARIA

One of the main pillars of prevention is vector control which may be by chemical control, biological control and personal protective measure taken up by individuals or community. Indoor residual spraying has been there for a long time but mosquitoes develop resistance to it. Aerosol spray at day time and fogging with malathion are other methods of chemical control. Use of mosquito larvivorous fish in tanks and other water bodies where mosquitoes breed are ways of biological control. Screening of home with wire mesh gives personal protection. As mosquito bites from dusk to dawn, evening use of repellent cream, coils and mats are effective in preventing bite and also wearing long sleeve clothes are helpful. Sleeping under insecticide treated bed-nets is very effective. Environmental management by reduction of breeding places, proper storage of water and reducing of unplanned construction will go in a long way to prevent mosquito breeding. Finally it is the participation of the community in these activities is essential.

Malaria Vaccine

Despite considerable effort it seems a good vaccine against malaria is far from reality. A number of liver-stage antigen including circumsporozoites protein of *P. falciparum* were developed as

vaccine candidate but none proved to be effective. Of the blood stage vaccine, SPf66 developed in Columbia which contains a mixture of synthetic peptides of sporozoites and ring infected erythrocytes showed some promise initially but failed in trials conducted in Africa. Transmission blocking vaccines directed against gametocytes are also in the line. Finally multistage vaccines are also under study but none of the report shows any hope in near future.

IN A NUTSHELL

1. Parasitological diagnosis is important for malaria diagnosis as it prevents unnecessary drug usage.
2. Microscopy is still the gold standard of diagnosis, rapid diagnostic tests (RDTs) are reserved for areas without skilled microscopist.
3. Complicated malaria needs prompt recognition as success of therapy decreases with time.
4. For uncomplicated *P. vivax* malaria, chloroquine is the drug of choice.
5. All cases of falciparum malaria should be treated with artemisinin combination therapy (ACT) irrespective of drug resistance status.
6. All cases of complicated malaria should be treated with either IV artemisinin or quinine irrespective of species.
7. IV artemisinin is superior to quinine for treatment of complicated malaria.
8. Mosquito control is still most effective in malaria prevention as vaccine against malaria is not available.

MORE ON THIS TOPIC

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Chapter 32.3

Leishmaniasis

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Leishmaniasis, a vector-borne disease, is caused by an obligate intracellular protozoan of the genus *Leishmania*, order kinetoplastida, family Trypanosomatidae, and is transmitted by the bite of female sandfly vectors. Clinical manifestations range from self-healing cutaneous ulcers to systemic multiorgan disease. It broadly manifests as visceral leishmaniasis (VL, also known as kala-azar), cutaneous leishmaniasis (CL) and mucocutaneous leishmaniasis (MCL).

EPIDEMIOLOGY

Leishmaniasis is endemic in 98 countries with more than 350 million people are at risk. Approximately 0.2–0.4 million VL cases and 0.7–1.2 million CL cases occur each year. More than 90% of global VL cases occur in just six countries: India, Bangladesh, Sudan, South Sudan, Brazil and Ethiopia. In India, about 100,000 cases of VL are estimated to occur annually and the state of Bihar accounts for more than 90% of cases. There has been a significant decline in the annual incidence of VL in India in recent years. CL is more widely distributed, with about one-third of cases occurring in each of the three regions, the Americas, the Mediterranean Basin and western Asia from the Middle East to Central Asia.

TRANSMISSION

The only proven vector of human disease is sandfly of species *Phlebotomus* (Fig. 1) in the Old World (Asia, Africa and Europe) and *Lutzomyia* in the New World (the Americas). Transmission is of two types: anthroponotic, where the vector transmits the disease from human to humans; and zoonotic where the disease is transmitted from an animal reservoir to humans. Most CL have zoonotic transmission except those caused by *L. tropica*, which is predominantly anthroponotic. Human to human transmission of VL through infected needles have been reported among IV drug users in the Mediterranean region. *In utero* transmission to the fetus can occur rarely.



Figure 1 A blood fed female sandfly *Phlebotomus argentipes*

LIFE CYCLE

The life cycle of *Leishmania* has two distinct forms: promastigotes (length 10–20 μm), flagellar form found in the gut of the sandfly vector; and an aflagellar amastigote form (length 2–4 μm), which develops intracellularly in the vertebrate host. Promastigotes are introduced through the proboscis of female sandfly into the skin of the host. The neutrophils are among the first host cell that takes up the promastigotes. After the neutrophils undergo apoptosis the parasites are taken up by the macrophages and dendritic cells. Here they transform into amastigotes by losing their flagella and multiply. During feeding on infected hosts the sandflies inoculate the amastigotes which transform into promastigotes in their midgut. They multiply and then migrate to the anterior midgut and can infect a new host during blood feed.

VISCERAL LEISHMANIASIS (KALA-AZAR)

Visceral leishmaniasis is caused by the *Leishmania donovani* complex: *L. donovani*, the causative organism of VL in the Indian subcontinent and Africa, and children comprise about half of the victims; *L. infantum* (*L. chagasi*) which causes VL in the Mediterranean Basin, Asia, Central and South America primarily a disease of children in these regions. In South Asia and the Horn of Africa, the predominant mode of transmission of VL is anthroponotic. Patients with VL and those with post-kala-azar dermal leishmaniasis (PKDL) are the major reservoirs for the transmission. In the Mediterranean, the Middle East and Brazil, VL is zoonotic, with the domestic dog as the most important reservoir host sustaining transmission.

Immunopathogenesis

Infection does not always result in clinical illness and majority control the infection by mounting a successful immune response. The ratio of incident asymptomatic infections to incident clinical cases varies. In India asymptomatic infection is nine times more frequent than symptomatic VL. The host specific cell-mediated immune (CMI) response has an important role in controlling the infection. Studies in mouse model have shown that resistance to acquired leishmanial infection is controlled by the production of interleukin-12 (IL-12) by antigen presenting cells and subsequent secretion of interferon (IFN) γ , tumor necrosis factor (TNF) α and other proinflammatory cytokines by the T helper 1 (T_H 1) subset of lymphocytes. Patients with active VL have a mixed T_H 1 and T_H 2 response with high levels of IL-10 promoting the disease.

The organs of the reticuloendothelial system are affected primarily leading to enlargement of the spleen, liver and lymph nodes, though lymphadenopathy does not occur in the Indian subcontinent. Bone marrow dysfunction resulting in anemia and leukopenia occurs early and is followed by thrombocytopenia.

Clinical Features

In endemic areas of East Africa and India, the highest incidence is in children and young adults. In Southern Europe, North Africa and West and Central Asia, children in the age group of 1–4 years were most affected however with the increase in human immunodeficiency virus (HIV)-VL coinfection in Europe about half the cases are now in adults. The incubation period is believed to be 2–3 months but may be up to 1 year or more, and the onset of the disease is usually gradual. The common symptoms are fever with chills and rigor, malaise, weight loss, anorexia and discomfort in the left hypochondrium. The common clinical signs are non-tender splenomegaly which is usually palpable by 2 weeks and may become huge as the illness progresses, hepatomegaly is usually moderate, and there is wasting and pallor of mucous membranes (Fig. 2). Lymphadenopathy occurs commonly except in the Indian



Figure 2 A child with visceral leishmaniasis with hepatosplenomegaly

subcontinent. Blackish discoloration of the skin of the face, hands, feet and abdomen can occur (the vernacular name, *kala-azar*, means *black fever* or *deadly fever*). In Sudan, rarely a cutaneous nodule or ulcer or a mucosal lesion may be present, containing *Leishmania*. Signs of malnutrition (edema, skin and hair changes) develop as the disease progresses. Anemia can be severe and may lead to congestive heart failure. Thrombocytopenia can lead to epistaxis, retinal hemorrhages, and gastrointestinal bleeding. Intercurrent infections such as measles, pneumonia, tuberculosis, bacillary and amebic dysentery are common. Herpes zoster, chicken pox, boils in the skin and scabies may also occur. VL is usually fatal if left untreated.

Post-Kala-azar Dermal Leishmaniasis

In the Indian subcontinent 5–15% patients (highest in Bangladesh) with VL develop a chronic form of dermal leishmaniasis characterized by hypopigmented macules, papules and/or indurated nodules (**Figs 3A and B**), which is called post-kala-azar dermal leishmaniasis (PKDL). The dermal manifestations occur 6 months to 3 years after the cure of VL and spontaneous resolution is rare in the Indian subcontinent. On the other hand



Figure 3A Nodular form of post-kala-azar dermal leishmaniasis showing multiple nodules over face

in East Africa especially Sudan, up to 60% patients may develop PKDL, and is seen concurrently with VL or immediately thereafter within 6 months. In most patients, the skin manifestations resolve spontaneously, and only in a small minority treatment is needed.

HIV-VL Coinfection

It is a growing problem and has been reported from more than 35 countries. HIV infection increases the risk of developing VL by 100–2,320 times in areas of endemicity, reduces the likelihood of a therapeutic response, and greatly increases the probability of relapse. Initially, HIV-VL coinfection was reported from the Mediterranean countries, but the number of cases is increasing in sub-Saharan Africa especially in Ethiopia, Brazil and the Indian subcontinent. VL promotes the clinical progression of HIV. The clinical features are usually similar to a classic VL patient in majority of instances, however, in about one-fourth of cases there may be unusual manifestation with involvement of uncommon sites, e.g., infiltration of skin, oral mucosa, gastrointestinal tract, lungs and other organs.

Laboratory Diagnosis

Parasite Detection

The demonstration of the amastigote form of the parasite by microscopic examination of aspirates from bone marrow, spleen or lymph node is the gold standard for the diagnosis of VL (**Fig. 4**). Although the specificity is high, the sensitivity of microscopy varies, being higher for spleen (93–99%) than for bone marrow (53–86%) or lymph node (50%). Culture of these tissue aspirates further increases the sensitivity. However, splenic aspiration can be complicated by life-threatening hemorrhage, and requires considerable technical expertise.

Serological Tests

Serological tests based on indirect fluorescence antibody (IFA), enzyme-linked immunosorbent assay (ELISA) or western blot have shown high diagnostic accuracy in most studies but are poorly adapted to field settings. The direct agglutination test (DAT) and the rK39-based immunochromatographic test (ICT) are two serological tests that have been specifically developed for field use. Both DAT and rK39 ICT have very high sensitivity and specificity for VL however, rK39 in India, has lower sensitivity in East Africa. In the Indian subcontinent rK39 ICT has



Figure 3B A female child with macular form of post-kala-azar dermal leishmaniasis showing multiple depigmented macules over abdomen

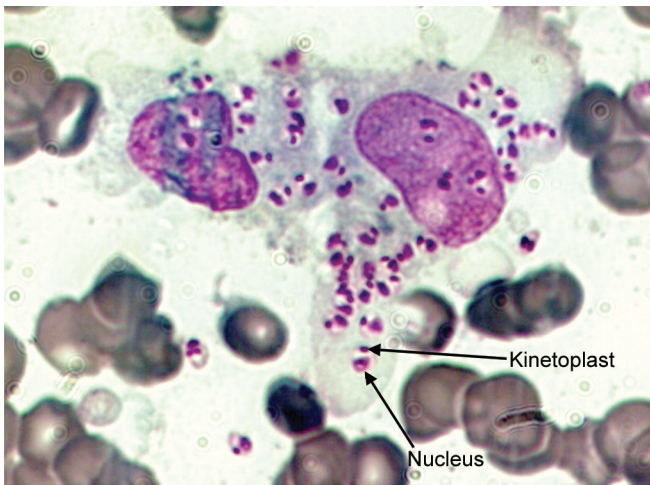


Figure 4 A microphotograph of splenic smear showing multiple amastigotes inside a macrophage. Inside amastigotes, larger light stained nucleus and small dark stained kinetoplast can easily be identified

become very popular as it is easy to perform, rapid, cheap, yields reproducible results, and can be performed with a drop of finger prick blood, in difficult field conditions.

Antibody-based tests have some drawbacks, serum antibody levels remain detectable up to several years after cure, and therefore, VL relapse cannot be diagnosed by antibody detection. They are often negative in HIV positive patient. Owing to asymptomatic infections, up to 32% healthy individuals, living in endemic areas with no history of VL, are positive for antileishmanial antibodies. Thus antibody-based tests must always be used in combination with a standardized clinical case definition for the diagnosis of VL.

Molecular Diagnosis

The detection of parasite deoxyribonucleic acid (DNA) by polymerase chain reaction (PCR) in blood or bone marrow aspirates is very sensitive but is currently restricted to only referral hospitals and research centers.

Hematological and Biochemical Parameters

Anemia and leukopenia occur earlier than thrombocytopenia. Hepatic transaminases are elevated commonly and serum bilirubin may be elevated occasionally. Hypergammaglobulinemia resulting in reversal of albumin globulin ratio is common.

Differential Diagnosis

Febrile illnesses like malaria, typhoid, tuberculosis, brucellosis, schistosomiasis and histoplasmosis can mimic VL. In an endemic region, fever with splenomegaly, pancytopenia and hypergammaglobulinemia strongly suggests the diagnosis of VL. In nonendemic regions history of travel to endemic area needs to be elicited.

Treatment

Once the diagnosis is established, patients should be started on antileishmanial drugs. In addition, supportive therapy like good nutrition, blood transfusion and treatment of intercurrent illnesses should be started.

Antileishmanial Drugs

Pentavalent antimonials (Sb^{V}) Sodium stibogluconate (100 mg/mL) and meglumine antimoniate (85 mg/mL) at the dose of

20 mg/kg body weight for 28–30 days has been the standard treatment for VL in most parts of the world. However, due to extensive drug resistance to Sb^{V} in Bihar, where the cure rate fell to less than 50%, it has been replaced by other drugs. Some common adverse events of Sb^{V} are metallic taste in mouth, arthralgia, myalgia, elevated hepatic and pancreatic enzymes. Cardiotoxicity—prolongation of QTc of more than 0.5 sec is an ominous sign, and may culminate into life-threatening cardiac arrhythmias. Antimonials are more toxic in HIV patients and a significant proportion of them have chemical pancreatitis.

Amphotericin B (AmB) It is a polyene antibiotic which is used for the treatment of antimony resistant VL in Bihar, India. It has excellent cure rates (~ 100%) at doses of 0.75–1.0 mg/kg for 15 days administered either daily or on alternate days. Adverse effects are very common include infusion reactions like high fever with rigor and chills, nausea, vomiting, thrombophlebitis. Serious and occasionally life-threatening adverse events include nephrotoxicity, hypokalemia and rarely hypersensitivity reaction, myocarditis, and bone marrow suppression.

Lipid formulations of AmB are rapidly picked up by the reticuloendothelial tissues, thus the amount of free drugs available is low leading to significantly decreased toxicity. This permits administration of large doses of the drug over a short period. Liposomal amphotericin B (AmBisome®; Gilead Sciences, USA; L-AmB), is the only US Food and Drug Administration approved AmB lipid formulation for VL. The total dose requirements of lipid formulations for treatment of VL vary from region to region. In India and Bangladesh, a single dose of 10 mg/kg results in a cure rate of more than 95%, and is currently one of the preferred treatments for VL in this region. In the Mediterranean region, Africa and South America a total dose of 18–21 mg/kg has been recommended. Recent studies suggest that L-AmB is not very effective in Sudanese patients.

Miltefosine An alkyl phospholipid, is the first oral antileishmanial agent, and is available as 10 mg and 50 mg capsules. It is registered for use in India since 2002 for the treatment of VL. It is the chosen drug for the VL elimination program in the Indian subcontinent (India, Nepal and Bangladesh). The recommended dose for children between 2 years and 11 years is 2.5 mg/kg for 28 days, for children 12 years and above 50 mg daily for those weighing less than 25 kg and 50 mg twice daily for those more than 25 kg for 28 days after meals. Cure rate is 94% in Indian children.

Adverse events include vomiting and diarrhea in 40% and 20% patients, respectively, and there may be asymptomatic elevation of liver enzymes. Rarely nephrotoxicity may occur. It has teratogenic potential and thus women of childbearing potential have to observe contraception for the duration of treatment and for an additional 3 months, due to its long half-life of approximately one week. Its long half-life also makes it vulnerable to the development of drug resistance. In a recent study from India, the efficacy of miltefosine appears to have declined and the relapse rate has doubled as compared to 2002. Efficacy of miltefosine in Nepal has been reported to be only 73%.

Paromomycin (PM, aminosidine) Paromomycin is an aminoglycoside-aminocyclitol antibiotic approved by the Indian government in 2006 for the treatment of VL. It should be used at a dose of 11 mg base/kg intramuscular (IM) injection daily for 21 days. It has a cure rate of 95% in the Indian subcontinent. The dose in other endemic regions has not been established. Pain at the injection site is the most common adverse event, whereas a small proportion of patients develop ototoxicity and rise in hepatic transaminases, both of which are completely reversible. Nephrotoxicity is rare. There is no data regarding its use in pregnancy. The main advantage of the drug is its low cost.

Multidrug Therapy

With growing resistance to antileishmanials, multidrug therapy is likely to be preferred in the future. The advantages are:

- Increased activity through use of drugs with synergistic or additive activity acting at different sites
- Shorter duration of therapy
- Lower dose requirement of individual drugs thereby decreasing toxicity and cost
- Preventing the emergence of drug resistance.

In a recent phase III study from India, single infusion of 5 mg/kg of L-AmB with either 7-day oral miltefosine or 10-day IM paromomycin; or 10 days each of miltefosine and paromomycin (with similar daily dose as in monotherapy) had excellent cure rates (>97% in all arms). In East Africa, the combination of sodium stibogluconate at 20 mg/kg plus paromomycin given at 15 mg/kg (11 mg base) for 17 days has shown excellent efficacy.

Treatment Guidelines

There are regional variations in dosage and duration of antileishmanial drugs. While a single dose of 10 mg/kg of L-AmB or combination therapy are the preferred treatment options in the Indian subcontinent, a combination of sodium stibogluconate with paromomycin for 17 days is treatment of choice in East Africa and Yemen. For Mediterranean Basin, Middle East, Central Asia and South America, L-AmB at a total dose of 18–21 mg/kg is recommended.

Post-Kala-azar dermal leishmaniasis In India, miltefosine for 12 weeks or amphotericin B 60–80 doses over 4 months are the recommended regimens for PKDL. In East Africa, PKDL is not routinely treated, as the majority of cases (85%) heal spontaneously within 1 year. Only patients with severe or disfiguring disease, those with persistent lesions (>6 months) or concomitant anterior uveitis and young children with oral lesions that interfere with feeding are treated. Sodium stibogluconate (20 mg/kg/day) for up to 2 months or a 20-day course of L-AmB at 2.5 mg/kg/day are used for these patients.

HIV-VL coinfection Liposomal AmB is the drug of choice for HIV-VL coinfection. A dose of 3–5 mg/kg/day intermittently for 10 doses (days 1–5, 10, 17, 24, 31 and 38) up to a total dose of 40 mg/kg is recommended but relapse is common. Secondary prophylaxis with L-AmB (5 mg/kg) every 3 weeks has been found to be useful in decreasing relapses. If L-AmB is not available, amphotericin B deoxycholate can be used. Antiretroviral therapy should be initiated immediately.

CUTANEOUS LEISHMANIASIS

Cutaneous leishmaniasis is caused by various *Leishmania* species. Up to 90% of cases of CL occur in Afghanistan, Algeria, the Islamic Republic of Iran, Saudi Arabia, the Syrian Arab Republic, Bolivia, Brazil, Colombia, Nicaragua and Peru. Based on its geographical distribution, CL can be divided into Old World (including southern Europe, the Middle East, parts of southwest Asia and Africa) and New World leishmaniasis (from Mexico and Latin America).

Old world CL is caused mainly by *L. infantum*, *L. tropica*, *L. major* and *L. aethiopica*. *L. tropica* causes anthroponotic CL and is found in areas ranging from western India to Turkey and parts of North and East Africa. *L. major* causes zoonotic CL in western and central Asia, North and sub-Saharan Africa, Kazakhstan, Turkmenistan and Uzbekistan where Nile rats, rodents and gerbils are the reservoir. *L. aethiopica* is endemic in Ethiopia, Uganda and Kenya, and causes zoonotic CL as well as diffuse cutaneous leishmaniasis (DCL) with hyraxes as their reservoir. *L. infantum* causes zoonotic CL in the Mediterranean Basin, Middle East,

Central Asia and China with dog as a reservoir. Cases of CL due to *L. donovani* have been reported from Cyprus, Israel and Sri Lanka.

New World leishmaniasis (from Mexico and Latin America) is caused predominantly by *L. mexicana* complex consisting of *L. amazonensis*, *L. mexicana*, *L. pifanoi* and subspecies *Viannia* consisting of *L. (V.) peruviana*, *L. (V.) guyanensis*, *L. (V.) panamensis*, and *L. (V.) braziliensis*.

Immunopathogenesis

In most patients T_H1 response results in asymptomatic or subclinical infection however it can lead to ulcerative skin lesions in some individuals. In those with skin lesions CD4 and CD8 T-cell IFN- γ and TNF- α producing lymphocytes, macrophages and B-cells constitute the majority of infiltrating cells. IL-10 and IL-13 have been associated with chronic lesions.

During active destruction of parasites in the skin there is edema in the superficial dermis and damage to collagen and elastin, with an increase in reticulin, followed by fibrosis.

Clinical Features

At the site of sandfly bite a papule or nodule appears after a few days or weeks which grow slowly. A crust then forms over it which may fall away, leading to an ulcer up to 5 cm in diameter with a raised edge and variable surrounding induration (**Fig. 5**). Small satellite lesions may develop just outside the ulcer or plaque. The lesions may be single or multiple and heal gradually over 2–15 months leaving a pigmented scar. Lymph node enlargement can occur. Lesions due to *L. major* and *L. mexicana* heal faster as compared to *L. tropica* and subspecies *Viannia*.

L. tropica can cause a chronic form of CL called leishmaniasis recidivans, also known as lupoid or tuberculoid leishmaniasis that may last for many years. New scaly erythematous papules and nodules arise in the center or periphery of a healed lesion. Skin biopsy demonstrates few parasites, but with a robust granulomatous, cell-mediated immune response. Untreated, the disease is destructive and disfiguring.

Lesions on the ear called chiclero ulcer (**Fig. 6**) is a self-healing sore caused by *L. mexicana*. *L. aethiopica* can at times give rise to oronasal leishmaniasis, which may distort the nostrils and lips.

Diagnosis

Demonstration of amastigotes from slit skin smears, aspirates, biopsies is the gold standard. Culture from a biopsy sample can be



Figure 5 A patient with cutaneous leishmaniasis with two ulcers with elevated margins and inflammation in and around the ulcers



Figure 6 A patient with chiclero ulcer with extensive lesions on the ear

done. PCR based detection of parasite nucleic acids improves the diagnostic sensitivity and allows identification of the *Leishmania* species. Speciation is particularly important in regions where several *Leishmania* species coexist as there is species specific variation in clinical outcomes and responses to treatment. CL needs to be differentiated from cutaneous tuberculosis, leprosy, fungal infections and malignant ulcers.

Treatment

Treatment recommendations of CL vary according to the infecting species and geographical region. For old world CL, local wound care with careful follow-up are indicated and spontaneous healing occurs in most patients. However, in persistent lesions local therapy is indicated, but if the patient has multiple lesions; large ulcers (≥ 5 cm in diameter); lesions over face, joints, toes, fingers, disfiguring lesions, systemic therapy is given. Patients with HIV coinfection also receive systemic therapy (**Box 1**). In the New World CL, self-healing is less common and some may develop diffuse disease thus antileishmanial treatment is usually given. CL caused by species associated with mucosal leishmaniasis (subgenus *Viannia*—*L. braziliensis* and *L. panamensis*), are given systemic therapy (**Box 2**).

Diffuse Cutaneous Leishmaniasis

Diffuse cutaneous leishmaniasis (DCL) is rare in children, and is a severe and rare form of CL caused by *L. aethiopica* in Ethiopia, *L. mexicana* and *L. amazonensis* in South and Central America. DCL is characterized by abundant parasites in the lesions with low or absent cell-mediated immune responses and an absence of delayed hypersensitivity to leishmanin skin test antigen. Patients have low or absent IFN- γ production by peripheral blood mononuclear cells and high concentrations of TNF- α , IL-10, IL-4, transforming growth factor β (TGF- β). It is characterized by widely disseminated cutaneous macules, papules, nodules or plaques, and by diffuse infiltration of the skin, especially on extensor surfaces of the limbs and on the face, where thickening of the eyebrows and ear lobes may resemble lepromatous leprosy. There is no ulceration. Mucosal involvement is confined to the borders of the nostrils and lips. This disease does not heal spontaneously, and relapses are frequent after treatment.

Mucocutaneous Leishmaniasis

Mucocutaneous leishmaniasis (MCL) is a disease of adults and extremely rare in children. It is caused by New World *Leishmania*

BOX 1 Recommended treatment regimens for Old World cutaneous leishmaniasis (CL) with grade of evidence (not ranked by preference)

Local therapy

• *L. major*:

- 15% PM/12% methylbenzethonium chloride (MBCL) ointment BID for 20 days (A)
- Intralesional antimonials, 1–5 mL per session plus cryotherapy (liquid nitrogen: 195°C), both every 3–7 days (1–5 sessions) (A)
- Thermotherapy, 1–2 sessions with localized heat (50°C for 30 sec) (A)
- Intralesional antimonials or cryotherapy independently, as above (D)

• *L. tropica*, *L. aethiopica** and *L. infantum**

- 15% PM/12% MBCL ointment, as above (D)
- Intralesional antimonials plus cryotherapy, as above (D)
- Thermotherapy, as above (A)
- Intralesional antimonials, alone, as above (B)
- Cryotherapy, alone, as above (C)

Systemic therapy

• *L. major*:

- Fluconazole, 200 mg/day oral for 6 weeks (A)
- 20 mg Sb^v/kg/day intramuscularly or intravenously for 10–20 days (D)
- 20 mg Sb^v/kg/day intramuscularly or intravenously plus pentoxifylline, 400 mg TID for 10–20 days (A)

• *L. tropica* and *L. infantum**

- 20 mg Sb^v/kg/day intramuscularly or intravenously for 10–20 days (D)
- 15–20 mg Sb^v/kg/day intramuscularly or intravenously for 15 days plus oral allopurinol 20 mg/kg for 30 days, to treat *L. recidivans* caused by *L. tropica* (C)

• *L. aethiopica*:

- 20 mg Sb^v/kg/day intramuscularly or intravenously plus PM, 15 mg (11 mg base)/kg/day intramuscularly for 60 days or longer to treat diffuse CL (C)

Abbreviations: Sb^v, pentavalent antimonials; PM, paromomycin.

Source: Control of the leishmaniasis. Report of a meeting of the WHO Expert Committee on the Control of Leishmaniases, 22–26 March 2010. WHO Technical Report Series 949. Grade A is the highest level of evidence.

*Few data are available on therapy for CL caused by *L. infantum* and *L. aethiopica*.

of subgenus *Viannia*—*L. braziliensis* and *L. panamensis* and rarely by *L. guyanensis* and *L. amazonensis*. Most cases are reported in Bolivia, Brazil and Peru. It is characterized by strong T_H1 response with high levels of IFN- γ and TNF- α , and strong delayed type hypersensitivity to leishmanin skin test. Intense inflammation causes extensive destruction of the tissues (**Fig. 7**). It can occur either simultaneously with cutaneous lesion or years later. It involves the mucosal tissues of the mouth and upper respiratory tract by lymphatic or hematogenous dissemination. Nasal lesions start with nodules and infiltration of nasal cartilage leading to obstruction and perforation. Mutilation of pharynx and larynx can also occur if left untreated. Local lymphadenopathy is frequent. MCL never heals spontaneously. Secondary bacterial infections are frequent, intercurrent pneumonia is the most common cause of death. Parasites are scarce in the lesional tissues and demonstration of parasite DNA by PCR is more sensitive.

Treatment of choice is pentavalent antimonials at the dose of 20 mg/kg for 30 days. Adding oral pentoxifylline at 400 mg/8 hour (in adults) to pentavalent antimonials for 30 days reduces the healing time significantly. Amphotericin B deoxycholate: 0.7–1 mg/kg by infusion every other day up to 25–45 doses can be given in relapsed cases. Liposomal amphotericin B at the dose of 2–3 mg/kg daily by infusion up to a total dose of 40–60 mg/kg is also considered adequate. In Bolivia, miltefosine at 2.5 mg/kg per day

BOX 2 Recommended treatment regimens for New World cutaneous leishmaniasis (CL) with grade of evidence

- Local therapy (all species)
 - 15% PM and 12% MBCL ointment BID for 20 days (B)
 - Thermotherapy: 1–3 sessions with localized heat (50°C for 30 sec) (A)
 - Intraleisional antimonials: 1–5 mL per session every 3–7 days (1–5 infiltrations) (B)
- Systemic therapy
 - *L. mexicana*
 - Ketoconazole: adult dose, 600 mg/day oral for 28 days (B)
 - Miltefosine: 2.5 mg/kg/day orally for 28 days (B)
 - *L. guyanensis* and *L. panamensis*
 - Pentamidine isethionate, intramuscular injections or brief infusions of 4 mg salt/kg/dose every other day for 3 doses* (C)
 - 20 mg Sb^v/kg/day intramuscularly or intravenously for 20 days* (C)
 - Miltefosine: 2.5 mg/kg/day orally for 28 days (B)
 - *L. braziliensis*
 - 20 mg Sb^v/kg/day intramuscularly or intravenously for 20 days (A)
 - Amphotericin B deoxycholate: 0.7 mg/kg/day, by infusion, for 25–30 doses (C)
 - L-AmB: 2–3 mg/kg/day, by infusion, up to 20–40 mg/kg total dose (C)
 - *L. amazonensis*, *L. peruviana* and *L. venezuelensis*
 - 20 mg Sb^v/kg/day intramuscularly or intravenously for 20 days
- Relapse treatment
 - Amphotericin B deoxycholate, as above
 - Sb^v: As above plus topical imiquimod every other day for 20 days (A)
 - L-AmB: 3 mg/kg/day, by infusion, up to 20–40 mg/kg total dose may be considered

Abbreviations: Sb^v, pentavalent antimonials; L-AmB, liposomal amphotericin B; PM, paromomycin.

*The efficacy of pentamidine and Sb^v depends on the geographical area.

Source: Control of the leishmaniasis. Report of a meeting of the WHO Expert Committee on the Control of Leishmaniases, 22–26 March 2010. WHO Technical Report Series 949. Grade A is the highest level of evidence.

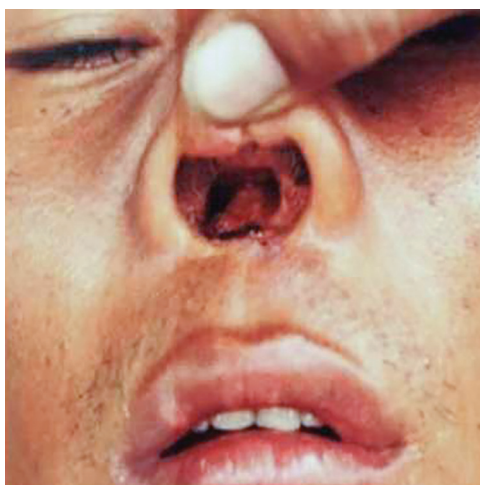


Figure 7 A patient with mucocutaneous leishmaniasis with extensive destruction of the nasal septum

orally for 4–6 weeks gives a cure rate of 70%. High cure rates are obtained when the disease is mild and lesions are limited to the nose and mouth. However, relapse and recurrence are frequent after clinical improvement and apparent cure when the larynx, vocal cords and trachea are involved. Thus regular follow-up of MCL, even after treatment which includes nasopharyngeal and laryngeal visualization, is essential.

PREVENTION

No vaccine is available for leishmaniasis. As prior infection confers some immunity against the infecting *Leishmania* species, leishmanization as a strategy is used in regions at risk for *L. major* infection. It consists of injecting viable parasites to produce a controlled skin lesion and induce T-cell immunity. Insecticide treated collars for dogs, vaccination and treatment of domestic dogs and culling of street dogs have been used to reduce *L. infantum* infection. Personal prophylaxis like protective clothing (as sandfly cannot penetrate clothes), use of insect repellent and bed nets are protective. Anthroponotic leishmaniasis is controlled by early case finding, treatment and vector control with residual insecticide spraying and use of insecticide impregnated bed nets.

IN A NUTSHELL

1. Leishmaniasis occurs in 98 countries throughout the world and in three major forms.
2. K39 antigen based rapid diagnostic tests are increasingly being used for the diagnosis of visceral leishmaniasis.
3. In Indian subcontinent liposomal amphotericin B or multidrug therapy are preferred treatment for visceral leishmaniasis; whereas in East Africa a 17-day combination therapy of pentavalent antimonials and paromomycin is the best option.
4. Liposomal amphotericin B is preferred in the Mediterranean region and for HIV-VL coinfection.
5. Liposomal amphotericin B, pentavalent antimonials or amphotericin B deoxycholate are the drugs recommended for New World VL.
6. Cutaneous leishmaniasis: Diagnosis is based on demonstration of amastigotes in tissue scrapings and speciation. Treatment varies with species and regions. Local treatment is preferred in old World cutaneous leishmaniasis.

MORE ON THIS TOPIC

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Chapter 32.4

Amebiasis

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Amebiasis is caused by the protozoa *Entamoeba histolytica* and usually presents with dysentery or diarrhea. The ameba may spread to various organs, the commonest being the liver where it manifests as amebic liver abscess. *E. histolytica* can be differentiated antigenically and by molecular methods from *Entamoeba dispar* which is nonpathogenic and responsible only for asymptomatic infection.

EPIDEMIOLOGY

E. histolytica has a worldwide distribution and is endemic in developing countries due to low socioeconomic conditions. It is the third leading cause of parasitic death in the world after malaria and schistosomiasis. It is estimated that approximately 10% of the world's population, i.e., 600 million people are infected, with an annual mortality of 40,000–110,000. Prevalence rates vary widely with the population studied, from around 1% in the industrialized nations to 50–80% in the tropics. The exact number of persons infected by pathogenic strains is still not clear but from the data available from a few such reports, the asymptomatic carriage seems to predominate with a prevalence of 10% and only 1% for pathogenic strains. In India, the prevalence rates vary from 5%–50% depending upon the population and geographical region.

ETIOLOGY

E. histolytica exists in nature in two forms: (i) cyst or (ii) a trophozoite (**Figs 1A and B**). Cysts are oval or round, asymmetrical with four nuclei. They are easily destroyed by most disinfectants and by heating to 55°C but may survive chlorination of water and in water at low temperature. Cyst is the infective stage of the parasite. Asymptomatic human cyst carriers are the principal reservoir of infection. There is no animal reservoir.

MODE OF SPREAD

The infection is transmitted by ingestion of food or water contaminated with fecal material containing cysts of *Entamoeba*. The source of contamination may be the food handlers or flies. The infective dose is less than 10 cysts. Cysts can remain viable and infective in water (even after chlorination) and feces for several days. They are thus potential agents for bioterrorism. Sexual transmission is also reported.

Young, immunocompromised and malnourished children and those receiving steroids are at a higher risk of severe *E. histolytica* infection. Other factors contributing to increased transmission

include low socioeconomic status, overcrowding, lack of piped water supply and poor sanitation. Recent research has shown increased genetic susceptibility to amebiasis in those with mutations of leptin receptor. Some protection is seen in children possessing the DQB1*0601 HLA allele genotype.

PATHOGENESIS

Following ingestion, cyst hatches in the small intestine to produce eight trophozoites. Trophozoites colonize and adhere to the colonic mucosa through a galactose and N-acetyl-D-galactosamine (Gal/GalNAc)-specific lectin which attaches to host cell receptors. This interaction generates a protective mucosal secretory IgA response. The trophozoites are also capable of inducing cytotoxicity of target cells or lymphocytes by introducing channels known as amebapores which are responsible for perforin mediated lysis. The protozoan has abundance of cysteine proteases which cause degradation of extracellular matrix of the host. The trophozoites multiply and spread laterally underneath the intestinal epithelium producing characteristic *flask-shaped or teardrop ulcers*. These lesions are commonly found in cecum, transverse colon and sigmoid colon. There is little local inflammatory response. Some ameba trophozoites become cyst and are passed in the stool to survive for weeks in a moist environment. On the other hand, some trophozoites invade the intestinal mucosa and spread via bloodstream to the liver, lung and brain.

Extraintestinal Complications

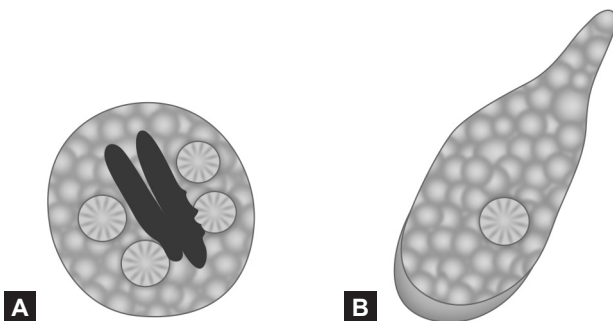
They arise from spread of infection through portal circulation. Amebic liver abscess forms because of toxin release and hepatocyte damage. It is seen more frequently in the right lobe of the liver (posterosuperior part); 5–20% have abscess in the left lobe. Single liver abscess is found in 95% of instances. Its contents are chocolate colored and viscid (described as anchovy-sauce appearance), usually sterile, and contain no neutrophils. Amebae are located at the periphery of abscess. The abscess may regress, rupture or disseminate. Transdiaphragmatic rupture of liver abscess into the pleural space may result in amebic empyema and pulmonary amebiasis. The abscess may also rupture into the peritoneum (2–5%) or pericardial cavity (<1%).

CLINICAL FEATURES

E. histolytica infection is asymptomatic in 90% of patients. About 4–10% of persons infected with *E. histolytica* develop amebic colitis, while less than 1% develop disseminated disease including amebic liver abscess. The intestinal involvement can result in acute illness like dysentery or bloody diarrhea, fulminating colitis, amebic appendicitis and ameboma of the colon.

Intestinal Disease (Amebic Colitis)

Incubation period for symptomatic disease varies from 2 weeks to months. Acute intestinal amebiasis presents with colicky abdominal pain, tenesmus and frequent loose stools containing mucus and blood. The stool may be positive for occult blood. Fever is seen in only one-third of patients and constitutional symptoms are rare (unlike bacillary dysentery). Examination may reveal diffuse tenderness in the cecal or rectosigmoid junction areas. The course of illness may be protracted lasting for weeks or even months. Rarely, a reactive collection of edematous granulation and fibrous tissue called an ameboma can grow into the lumen causing pain, obstruction and possibly, intussusception. Chronic amebiasis presents with intermittent diarrhea is often followed by constipation due to spasm of the large intestines, fatigue and weight loss. Toxic megacolon, pneumatosis coli (intramural air) and peritonitis can also occur. Acute amebic dysentery should



Figures 1A and B *Entamoeba histolytica*. (A) Cyst; (B) Trophozoite

be differentiated from that caused by *Shigella*, *Salmonella*, *Campylobacter*, *E. coli* and *Yersinia*.

Amebic Liver Abscess

It develops in less than 1% of infected persons, often months to years after exposure. A past history of amebic dysentery is forthcoming in only 20% of patients and only 10% have concomitant intestinal symptoms. The child presents with high fever with chills and rigors, abdominal pain, distension and tender hepatomegaly, and appears toxic. Pain in the upper abdomen is intense and radiates to the shoulder. Jaundice is uncommon and observed in only 10–15% cases. Abscess may rupture into pleural space, peritoneum and pericardium requiring emergency drainage. Mortality in children in ruptured abscess can be up to 25%. (refer Section 37 for further details on amebic liver abscess).

INVESTIGATIONS

Parasite Detection

Microscopic examination of formed stool for cysts or diarrheal stool for trophozoites is necessary for the diagnosis of intestinal infection with *E. histolytica*. Diarrheal stools must be examined within 1 hour of collection to look for motility of trophozoites. Stool microscopy cannot distinguish *E. histolytica* from *E. dispar* infection unless phagocytosed erythrocytes are seen in trophozoites (seen in *E. histolytica*). Stool antigen testing may also distinguish the two species. A complete examination of stool for cysts includes wet mount in saline, an iodine-stained wet mount and a fixed trichrome-stained preparation. Fixation of the smear is recommended as the trophozoites degenerate in unfixed smears. The stained preparations not only delineate cyst morphology but also distinguish bacillary from amebic dysentery. Stool contains plenty of erythrocytes but few leukocytes in patients with amebic colitis unlike bacillary dysentery where the inflammatory cells, especially polymorphonuclear cells are replete. Other stains like Giemsa, methylene blue, Ziehl-Neelsen or Wright stains can also be used as they delineate the nucleus well. At least three stool specimens taken on consecutive days should be examined to exclude amebic infection of the intestines since excretion of cysts may be intermittent. However, detection of amebic cysts, even with associated gastrointestinal symptoms does not necessarily indicate acute infection. Moreover, presence of contaminants, lack of expertise in detection by microscopy and delay in transport and processing the stool sample decrease the reliability of stool microscopy alone for diagnosis.

Few culture media have been used for isolation like Locke-egg media or TYI-S-33. The isoenzyme analysis is considered as *gold standard* which is done on culture samples and can differentiate pathogenic and nonpathogenic amebae. The culture yield is however unsatisfactory in most cases as maintenance of a protozoan culture is tedious and mixed growths are commonly encountered.

Serology

The usefulness of serological tests in intestinal amebiasis is limited due to high seropositivity rates in endemic areas. In extraintestinal amebiasis and invasive amebiasis, antibody detection by enzyme-linked immunosorbent assays (ELISA) is the most sensitive test. The detection of IgM is suggestive of recent amebiasis unlike IgG response. Indirect hemagglutination (IHA) test may be done for invasive intestinal disease or liver abscess which has shown good results in immunocompromised individuals. IHA is usually negative in asymptomatic carriers. Serological response as detected by counterimmunoelectrophoresis (CIE) or ELISA becomes negative 6–12 months after infection. IHA, on the other

hand, may stay positive for as long as 10 years following complete recovery. Recently, antigen based ELISA kits have been used for detection which have excellent sensitivity and specificity. These kits can differentiate *E. histolytica* from *E. dispar*. The kits are coated with monoclonal antibodies targeted against the serine-rich residue or Gal/GalNAc-specific lectin of *E. histolytica*. Besides detection in stools, the kits can also be used for detection of antigen in saliva, serum or abscess fluid. The only limitation of the kit is that it can be applied only on fresh samples and renders fixed smears unsuitable. Molecular based polymerase chain reaction (PCR) stool assays (conventional and real-time PCR) have been used in research settings. Their performance is affected by lack of uniformity, stringent temperature and transport requirements for DNA extraction and high chances of false-negative results due to contamination. A triage parasite panel impregnated with monoclonal antibodies against *Giardia*, *Cryptosporidium* and *Entamoeba* has also been developed. It is simple, convenient and has shown greater than 95% sensitivity and specificity on unfixed, fresh stool samples. However, it fails to differentiate between *E. histolytica* and *E. dispar*. **Table 1** shows the comparative performances of various diagnostic methods in intestinal amebiasis.

Imaging

Sigmoidoscopy followed by aspiration of mucosal lesions or biopsy is valuable in symptomatic sick patients where other tests fail to provide conclusive evidence.

Liver Aspirate

It is difficult to demonstrate the amebae in the liver aspirate. Trophozoites are sparse in the aspirate and can be demonstrated only from the wall of the abscess.

Others

Leukocytosis, anemia, high erythrocyte sedimentation rate (ESR) and elevated alkaline phosphatase are common in amebic liver abscess. There is no eosinophilia in invasive disease.

TREATMENT

Due to the possibility of its invasive nature and severe extraintestinal manifestations, all children with *E. histolytica* infection, whether symptomatic or not, should be treated. Luminal amebicides, such as diloxanide furoate and iodoquinol, act on only those organisms that are present in the intestinal lumen. Tissue amebicides, such as metronidazole, tinidazole, chloroquine and dehydroemetine, are effective in the treatment of invasive amebiasis but are less effective for luminal clearance. A combination of a luminal and a tissue amebicide is thus advocated for complete parasite clearance in invasive disease. Metronidazole is the most popular drug for management of both intestinal and extraintestinal forms of

Table 1 Diagnostic tools for intestinal amebiasis

Diagnostic method	Sensitivity	Specificity
Stool microscopy	<60%	10–50%
Serum antibody (ELISA)	>90%	>85%
Serum antigen (ELISA)	65%	>90%
Stool antigen (ELISA)	>95%	>95%
Stool PCR	>70%	>90%

Abbreviations: ELISA, enzyme-linked immunosorbent assays; PCR, polymerase chain reaction.

Adapted from Tanyuksel M, Petri WA. Laboratory diagnosis of amebiasis. Clin Microbiol Rev. 2003;16(4):713–29.

amebiasis, and till date there is no evidence of resistance against this agent.

Invasive amebiasis (both intestinal and extraintestinal) should be treated initially with a tissue amebicide like: (i) oral metronidazole 35–50 mg/kg/day in three divided doses for 7–10 days or (ii) tinidazole 50 mg/kg/day once daily for 3–5 days. Tinidazole is as efficacious as metronidazole but the treatment duration is shorter with fewer adverse effects. Following this all children should be given a course of luminal amebicide: (i) diloxanide furoate 20 mg/kg/day in three divided doses for 7 days, (ii) paromomycin 25–35 mg/kg/day in three divided doses for 7 days or (iii) iodoquinol 30–40 mg/kg/day in three divided doses for 20 days. Either of paromomycin, diloxanide furoate or iodoquinol may be used to treat asymptomatic carriers, given in the regimen same as for invasive disease. Reinfection is quite common even after complete cure. For cases of *fulminant amebic colitis*, therapy with dehydroemetine (1 mg/kg/day subcutaneously or IM), may be instituted. Broad spectrum antibiotics may also be needed. Intestinal perforation or ruptured amebic liver abscess or toxic megacolon may warrant surgical intervention.

PREVENTION

Prevention involves avoiding fecal contamination of food and water and adopting good handwashing technique. Boiling and purification of drinking water by filtration is an important preventive measure. The use of night soil (human feces) for fertilization of crops should be avoided.

AMEBIC MENINGOENCEPHALITIS

There are three genus of free living amebae which are implicated in human disease namely: *Naegleria*, *Acanthamoeba* and *Balamuthia*. The former is associated with rapidly progressive acute meningoencephalitis while the illness caused by the latter two runs a more indolent course.

Primary Amebic Meningoencephalitis

Naegleria fowleri is the causative agent of primary amebic meningoencephalitis (PAM) which is characterized by a rapidly progressive fatal course. The parasite resides in warm water. The life cycle includes two forms: (i) trophozoite and (ii) cyst. The infection is frequently acquired from contaminated swimming pools or lakes and reaches the brain via the olfactory epithelium of the nose. Histological changes in the brain include edema, hemorrhage, necrosis and hyperemia of meninges. There is purulent exudate throughout the brain parenchyma, more so over the gray matter. The incubation period is short (2–7 days) which is followed by fever, malaise, seizures and signs of meningoencephalitis. The clinical presentation closely resembles that of acute pyogenic meningitis. The survival rates are poor due to severity of illness and difficulty in establishing a timely diagnosis. The cerebrospinal fluid (CSF) shows neutrophilic predominance, elevated proteins and reduced sugar levels. The diagnosis is confirmed by demonstration of motile trophozoites on a wet mount of CSF (which may be mistaken for atypical mononuclear cells). Molecular diagnostic techniques may also be used in high cases of suspicion. Imaging is seldom helpful as it may show nonspecific changes or mild edema with basilar meningeal enhancement. The disease is fatal in most cases. As per data from Centers of Disease Control and Prevention (CDC), the mortality rate of PAM was 129/132 cases in US alone from 1962–2008. Amphotericin-B, rifampicin and fluconazole have been used for treatment. Steroids have been tried in some patients with undefined benefit. Miltefosine is recently approved by CDC for treatment of free living amebae. Among the very few survivors, sequel like hydrocephalus and delayed development has been noted.

Granulomatous Amebic Meningoencephalitis

Granulomatous amebic meningoencephalitis (GAM) is caused by *Acanthamoeba*, a ubiquitous ameba found in soil, dust, untreated or distilled water, swimming pools and other domestic environments. The organism derives its name by the virtue of presence of spike-like structure (acanthopodia) on its surface. Almost 20 species of *Acanthamoeba* are known which are subgrouped into three groups. Organisms of group II are most abundant and most pathogenic to humans. *Acanthamoeba* is frequently associated with keratitis in immunocompetent hosts, especially among contact lens users. Besides keratitis, it also causes subacute granulomatous dermatitis, sinusitis, pneumonitis, disseminated disease and a chronic meningoencephalitis which has been described as granulomatous amebic encephalitis (GAE) due to its histological picture. GAE is a rare and fatal illness which is commonly seen in immunocompromised individuals. Almost 1.57 deaths per 10,000 HIV/AIDS deaths have been attributed to GAE. The organism exists in two forms: (i) active trophozoite and (ii) a dormant cyst stage. Their virulence is predominantly due to release of proteases. The most common portal of entry is the respiratory route which results in hematogenous spread in immunocompromised individuals. The clinical presentation and course of GAE is almost similar to tubercular meningitis. Another differential diagnosis to be considered is cryptococcal meningitis. The CSF picture is also similar showing elevated proteins and lymphocytic pleocytosis. The diagnosis of GAE is confirmed by demonstration of trophozoites in CSF. In vivo confocal microscopy or examination of contact lenses can be done for detection of *acanthamoeba* keratitis. Alternately, immunofluorescence assays and multiplex real-time PCR are also available, though their use is limited by cost and availability. Serological tests may be used to identify antiacanthamoeba antibodies. Imaging of the brain may detect ring-enhancing, space-occupying lesions in GAE. The treatment is largely empirical as no specific drug therapy has been found useful. The treatment options include drugs like pentamidine, flucytosine, ketoconazole and amphotericin B. A combination of voriconazole and miltefosine has shown promising results. Both these drugs have good central nervous system (CNS) penetration and better safety profiles.

Balamuthia Mandrillaris

Balamuthia mandrillaris is a free living ameba implicated in meningoencephalitis which presents as a subacute or chronic illness. The disease is rare, affects children and elderly and is difficult to diagnose. The disease is seen among transplant patients also. The protozoan is found in soil and water and is transmitted by contamination of skin wounds or by aspiration. It commonly results in painless skin ulcers, chronic sinusitis and pneumonia. The trophozoites can spread hematogenously to CNS manifesting as fever, personality changes, headache, focal seizures, cranial nerve or motor deficits. Almost a quarter of such patients have preceding skin lesions at presentation. The detection of trophozoites in CSF is difficult which may reveal only lymphocytic pleocytosis with elevated proteins. Imaging of the brain may show solitary or multifocal mass-like lesions with ring enhancement, edema and hydrocephalus. Trophozoites can be detected in the skin biopsy which show granulomatous inflammation and vasculitis. Molecular diagnostic techniques, like indirect immunofluorescence (IIF), immunohistochemistry (IHC) or PCR, yield better diagnostic results and can differentiate *Balamuthia* from *Acanthamoeba*. A combination of azoles or amphotericin B with a macrolide has shown good survival rates. Other agents which have been tested as efficacious include pentamidine, polymyxin B, albendazole, sulfadiazine, flucytosine and miltefosine. Surgical debulking in case of large lesions is sometimes necessary.

IN A NUTSHELL

1. *E. histolytica* is a common protozoan infecting the humans which frequently causes dysentery.
2. The protozoa may spread hematogenously to result in hepatic abscess.
3. Stool microscopy is the simplest tool to differentiate intestinal amebiasis from bacillary dysentery, but lacks sensitivity and specificity.
4. All infected children should be treated whether symptomatic or not.
5. Treatment of choice is metronidazole. A luminal amebicide should be added for complete eradication.
6. Free living amebae can cause meningoencephalitis in humans either a rapidly progressive acute form (PAM) caused by *Naegleria* or a chronic granulomatous form (GAE) caused by *Acanthamoeba*.
7. Diagnosis of PAM or GAE requires high index of suspicion. Survival depends on timely diagnosis and appropriate therapy.

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Chapter 32.5

Giardiasis

Aashima Dabas, Piyush Gupta

Giardia lamblia (also known as *G. intestinalis* or *G. duodenalis*) is an important flagellated protozoan enteropathogen of humans and mammals. It affects 2.5 million people annually and is one of the most common parasite infections of humans worldwide. The clinical manifestations range from asymptomatic carrier state to acute and persistent diarrhea and malabsorption syndrome. There are five other species of *Giardia* namely: (i) *G. agilis*, (ii) *G. ardeae*, (iii) *G. muris*, (iv) *G. microti* and (v) *G. psittaci*, which infect various animals and are nonpathogenic to man.

EPIDEMIOLOGY

According to estimates by the World Health Organization (WHO), almost 1 billion people are infected with giardiasis, of which 25 million die annually. It is now included in the *WHO Neglected Disease Initiative*. The protozoan is a commoner occurrence in developing countries (prevalence rate 20–30%) as compared to the developed countries which report prevalence as less as 2–5%. During giardiasis surveillance from 2006–2008, almost 19,000 new cases were documented by the Centers for Disease Control and Prevention (CDC) in USA alone.

Agent

The parasite exists in the form of trophozoites or cysts (**Figs 1A and B**). Trophozoites colonize the proximal small intestine. Cysts are excreted in the feces; these are the infective stage of the parasite. There are eight genotypic assemblages (A to H) for *G. lamblia*. The human are infected with assemblage A or B while the rest assemblages infect dogs, cats and other household pets. Both A and B genotypes have also been isolated among other mammals.

Host Factors

Children appear to be more severely affected than adults. The infection is generally self-limited in immunocompetent children and adults. Humoral immunodeficiency is associated with chronic *Giardia* infection. Children with undernutrition and cystic fibrosis are particularly predisposed to giardiasis. Breastmilk contains glycoconjugates and secretory IgA that protect against giardiasis.

Children in frequent contact with livestock and other animals also have higher predisposition to infection.

Environmental Factors

Man and contaminated water supply remain the major reservoirs of *Giardia*. Giardiasis is spread by fecal-oral contamination, the prevalence being higher in populations with poor sanitation, close contact, and oral-anal sexual practices. Thus, a seasonal trend toward frequent outbreaks from June to October has been seen. The disease is commonly waterborne because *Giardia* is resistant to the chlorine levels in normal tap water. Foodborne transmission is rare but can occur with ingestion of raw or undercooked foods. There is a risk of zoonotic transmission of *Giardia* reported from dogs, cats and cattle. This transmission has been found bidirectional in some cross-sectional surveys, suggesting the possibility of *reverse zoonosis*, wherein human specific *Giardia* assemblages were isolated from animals.

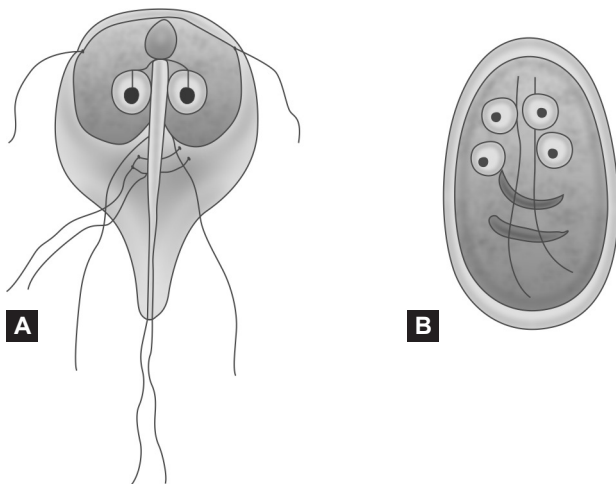
PATHOGENESIS

The life cycle of *Giardia* consists of two stages: (i) the fecal-orally transmitted cyst and (ii) the disease-causing trophozoite. Cysts are passed in a host's feces, remaining viable in a moist environment for months. Ingestion of at least 10–25 cysts can cause infection in humans. When a new host consumes a cyst, the host's acidic stomach environment stimulates excystation. Each cyst produces two trophozoites.

Each trophozoite has four pairs of flagella and two nuclei. The trophozoites carry a ventral disk on its concave surface which enables their attachment to the intestinal wall. These trophozoites migrate to the duodenum and proximal jejunum, where they attach to the mucosal wall by means of a ventral adhesive disk and replicate by binary fission. The flagella of the trophozoite mediate its transport and account for its virulence. In addition to the adhesive disk, the trophozoite also uses complex cytoskeletal contractile network comprised of giardin proteins and microtubular proteins for host cell contact. Growth of trophozoites is promoted by bile, glucose and relative hypoxia. The powerful sucking disk of the trophozoite causes mechanical irritation and damage to the microvilli of the small bowel mucosa resulting in deficiency of brush border enzyme activities. The trophozoite attachment also stimulates an inflammatory cascade by activating intracellular caspases, ultimately resulting in cell apoptosis. This results in malabsorption of sodium and glucose and hypersecretion of chloride which manifests as diarrhea. The trophozoite is capable of wide antigenic variations which help it to evade the host immune system resulting frequently in persistence of infection.

As the detached trophozoites pass through the intestine, they undergo encystation to form oval cysts containing four nuclei. Cysts pass in stools of infected persons and can remain viable for up to 2 months in soil. Unlike amebiasis, there are no invasive or locally destructive lesions in the intestines. The following pathological changes are evident in intestines in giardiasis: intestinal cell apoptosis, crypt hyperplasia, diffuse shortening of brush border and increased mucus production. Functional impairments include intestinal hypermotility, anion hypersecretion, brush border enzyme deficiencies and malabsorption.

Parenchymal involvement of the pancreas has been incriminated for the reported steatorrhea and decreased trypsin activity. Fat malabsorption in giardiasis can also be attributed to bacterial overgrowth in the duodenum and upper jejunum and bile salt deconjugation liberating free bile acids. Immunological studies have shown decreased levels of secretory IgA in duodenal aspirates and depressed T-cell function. Interestingly, prolonged infection with *Giardia* may offer cross-protection against other enteropathogens. It is postulated that repetitive attachment of



Figures 1A and B *Giardia lamblia*. (A) Trophozoite; (B) Cyst

the trophozoite makes the intestinal epithelium unfavorable for attachment by other organisms. In addition, there is activation of host immune responses like secretion of lactoferrin, defensin, secretory IgA and epithelial mucin, which are protective.

CLINICAL FEATURES

Intestinal Giardiasis

Asymptomatic carriage is the most common form of infection. In *symptomatic cases*, incubation period after ingestion of cysts is 1–2 weeks. In *acute infections*, there may be a sudden onset of explosive watery (nonbloody) foul smelling diarrhea along with abdominal distension, flatulence, nausea, anorexia and epigastric cramps. There is no blood or mucus in stools. The illness may last 3 or 4 days and is usually self-limiting in normal immunocompetent children.

Some infections may have a *subacute onset* with a protracted course, with persistent or recurrent mild to moderate symptoms such as brief episodes of loose foul-smelling stools accompanied by flatus and abdominal distension. Between exacerbations, the stools are mushy or there may be constipation. Abnormal stool pattern may alternate with normal bowel movements. Symptoms last for 2–4 weeks.

Thirty to fifty percent children develop *persistent diarrhea*. Children with chronic giardiasis show lactose malabsorption, steatorrhea, iron deficiency anemia and failure to thrive. Unlike *E. histolytica* infection, there is no extraintestinal spread of infection. Giardiasis is also a frequent cause of Traveler's diarrhea (commonest being *Escherichia coli*) where there is history of travel to an endemic country. The diarrhea is prolonged (>7 days) or persistent (≥14 days). A subset of patients may develop long-term complications like postinfectious irritable bowel syndrome and rarely cancer of pancreas or gallbladder.

Extraintestinal Manifestations

Almost one-third of patients suffering with giardiasis may exhibit an extraintestinal complication as enlisted in **Table 1**. The causative mechanisms are still obscure and represent interplay of host and agent factors.

INVESTIGATIONS

Diagnosis is made by examining diarrheal stools for trophozoites or cysts. At least three specimens of stools collected on alternate days (detection rate 90%) are examined microscopically because the multiplication and passage of the giardial cysts is often intermittent. Sensitivity of a single stool examination is only 50%. Stool does not contain blood or leukocytes. Trophozoites are usually seen only in watery diarrhea but can also be detected by endoscopic brush cytology or intestinal biopsy. A duodenal aspirate or biopsy may

yield high concentration of *Giardia*. Biopsy of the duodenum is not routinely recommended but may be done in patients with clinically suspected giardiasis, negative stool tests, negative duodenal fluid aspirate, absent secretory IgA level, hypogammaglobulinemia, abnormal lactose tolerance test or achlorhydria. Another test may be recommended if the microscopic examination of stool is negative, viz. the *string test*. A weighted piece of string is swallowed till it reaches the duodenum. The trophozoites adhere to the string and may be visualized microscopically after withdrawal of the string.

Stool enzyme immunoassay (EIA) or direct immunofluorescence tests for *Giardia* antigens are the preferred tests for diagnosis. Blood cell counts are normal. There is no eosinophilia as there is no tissue invasion. Newer diagnostic tools [polymerase chain reaction (PCR) based] using molecular analysis of small subunit ribosomal RNA (SSU rRNA), *gdh*, *tpi* and *bg* genes of *Giardia* are under development.

TREATMENT

All symptomatic cases—acute and persistent diarrhea, failure to thrive and malabsorption syndrome require drug treatment. Few protocols mention treatment of asymptomatic carriers also. However, due to higher reinfection rates and predisposition to drug resistance in endemic areas, asymptomatic cyst carriers are not treated except during outbreaks.

The following classes of drugs are available for treatment; the doses are summarized in **Table 2**. The drug of choice may be tinidazole or nitazoxanide.

- **5-Nitroimidazoles (5-NI)** These include metronidazole, tinidazole, secnidazole and ornidazole. These drugs chiefly affect the protozoal electron transport. Tinidazole has very high efficacy (>90%) and suffices as a single-dose therapy. However, high cost limits use in mass campaigns. Metronidazole is a cheap and effective alternative. It requires frequent dosing which affects compliance and is associated with side effects like nausea and metallic taste. There is early evidence of carcinogenicity in animal models with use of metronidazole. Few recent reports of drug resistance and rapid reinfection in endemic areas have been reported with its use.
- **Benzimidazoles** Albendazole and mebendazole act by disrupting the tubulin in cytoskeleton of *Giardia*.
- **Nitrothiazolyl-salicylamide derivative** Nitazoxanide inhibits the growth of trophozoites by interfering with enzymes required for anaerobic metabolism. This is a highly effective antiprotozoal drug with limited side effects like abdominal pain and headache. Its safety is not established in infants.
- **Miscellaneous** Furazolidone and quinacrine. Auranofin is a gold containing cysticidal compound, recently approved for use in giardiasis.

Table 1 Extraintestinal complications of giardiasis

System	Complication/manifestation
Ocular	Iridocyclitis, choroiditis, retinal hemorrhages, salt and pepper retinal degeneration
Musculoskeletal	Reactive arthritis or asymmetric synovitis usually of the lower extremities, hypokalemic myopathy, muscle necrosis, chronic fatigue syndrome
Immunological	Predisposition to allergies manifesting as rashes or urticaria
Nutritional	Wasting, undernutrition, stunting, iron deficiency anemia, micronutrient deficiencies
Miscellaneous	Impaired cognitive decline, lower intelligence quotient, poor language cognition and impaired psychomotor development

Table 2 Treatment of giardiasis in children

First-line therapy	
Tinidazole	>3 years: 50 mg/kg, single dose, oral
Nitazoxanide	1–3 years: 100 mg BD for 3 days, oral 4–11 years: 200 mg BD for 3 days, oral >12 years: 500 mg BD for 3 days, oral
Metronidazole	15 mg/kg/day in three divided doses for 5–7 days
Second-line therapy	
Albendazole	>6 years: 400 mg once a day for 5 days
Furazolidone	6 mg/kg/day in four divided doses for 10 days
Quinacrine	6 mg/kg/day in three divided doses for 5 days

Note: Paromomycin is not indicated for treating giardiasis in children.

PREVENTION

The infection can be prevented by adopting safe sanitary practices, regular handwashing and proper disposal of human and animal waste. Since the disease is primarily water borne, contamination of surface water should be minimized and safe potable water should be made available.

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IN A NUTSHELL

- Giardiasis is a common parasitic infection of humans.
- It is primarily spread by fecal-oral route through contaminated water supply.
- Clinical spectrum consists of asymptomatic cyst carriers, explosive diarrhea, subacute protracted course with GI symptoms and persistent diarrhea.
- Diagnosis is by stool microscopy of at least three samples; stool EIA is the preferred serological test for detection of *Giardia* antigen.
- Asymptomatic cyst carriers need not be treated routinely.
- Tinidazole or nitazoxamide are the drug of choice for symptomatic cases.

Chapter 32.6

Cryptosporidiosis

Aashima Dabas, Piyush Gupta

Cryptosporidiosis, caused by *Cryptosporidium* spp. primarily presents as watery diarrhea. Children less than 2 years and immunocompromised children, especially those with HIV infection and AIDS are prone to this infection. The organism was first isolated from humans in 1976. The infection is ubiquitous worldwide and higher prevalence rates are seen in developing countries (mean 6.1%) than the developed nations (mean 2.2%).

EPIDEMIOLOGY

Agent

Cryptosporidium is a protozoan parasite of the apicomplexa phylum with 16 species. The two species implicated in human disease are *Cryptosporidium hominis* and *Cryptosporidium parvum*. The former is isolated frequently in human infections in developed countries, while the latter is seen more often in developing countries or in zoonotic infections in developed nations. *C. hominis* results in greater severity of diarrhea and results in more growth faltering than *C. parvum*. The former species is also associated with extraintestinal complications like arthralgia, headache, fatigue and ocular pain, unlike the latter.

Host Factors

The mean prevalence is higher in immunocompromised individuals of both developing countries (24%) and developed countries (14%) than that reported in healthy individuals. Both congenital immunodeficiency states (especially severe combined immunodeficiency syndrome, X-linked hyperimmunoglobulin M syndrome and CD4 lymphopenia) and acquired immunocompromised states like HIV and bone marrow transplant recipients are predisposed to the infection. The prevalence is more in extremes of age-childhood and old-age. Breastfeeding has not shown to be protective. The cell-mediated immunity is the primary defense mechanism; humoral immunity has limited role.

Environmental Factors

Cattle, a known reservoir for *C. parvum*, and has been implicated in various outbreaks. The oocysts are susceptible to desiccation and do not survive well at high temperatures but resistant to routine chlorination of water. Prolonged bright sunlight and exposure to ultraviolet B rays are germicidal. The role of repeated exposures to *Cryptosporidium* spp. in imparting protective immunity to humans is also hypothesized. Higher levels of anti-cryptosporidium antibodies were detected in those with repeated infections.

The Global Enteric Multicenter Study (GEMS) is a 3-year, prospective, age-stratified, case control study conducted in children aged 0–59 months to evaluate the epidemiology of moderate to severe childhood diarrhea, across sub-Saharan Africa and South East Asia at seven sites. *Rotavirus* was the most common isolated microbe, which was closely followed by *Shigella*. Surprisingly, *Cryptosporidium* has been isolated as second most common pathogen at five sites.

PATHOGENESIS

The infection is chiefly acquired by feco-oral route through ingestion of oocysts from contaminated water. Other modes of transmission include person-to-person (outbreaks or at day

care centers and hospitals), food-borne and zoonotic spread. Inhalational mode of transmission has been reported in immunocompromised patients causing laryngotracheitis and mild diarrhea. The infective dose is low—10–83 oocysts for *C. hominis* and 132 oocysts for *C. parvum*. The ingested oocysts excyst in the small intestine and release four sporozoites each. These sporozoites demonstrate gliding motility, during which they deposit various proteins required for attachment and invasion into the host cell. After invasion of enterocytes, a parasitophorous vacuole is formed within the apical cells of intestine. The sporozoites mature into trophozoites which cause modifications of the host actin cytoskeleton of intestinal epithelial cells and alterations in host-cell apoptosis. They divide by asexual reproduction to produce merozoites. Few merozoites may differentiate into gametocytes to form a zygote, which divides by meiosis to produce oocysts. The thin-walled oocysts are implicated in auto-infection and the thick-walled oocysts are excreted to infect other hosts.

CLINICAL FEATURES

The infection presents with nonbloody watery diarrhea following an incubation period of 2–12 days. The symptoms may start even before oocysts are excreted. Vomiting may be seen in more than 80% of infected children. Fever occurs in about 50% of infected children. The disease is usually self-limiting in immunocompetent children, though oocysts may be shed for months, seen as asymptomatic carriage. In immunocompromised patients, severe constitutional symptoms like abdominal cramps, nausea, vomiting, and fever may be observed. They are at risk of more severe and fulminant disease course which may result in death. *Cryptosporidium* frequently results in persistent diarrhea in malnourished children. It may also cause serious affection of the biliary tract and pancreas manifesting as sclerosing cholangitis, acalculous cholecystitis, and/or pancreatitis. Rarely respiratory tract involvement may cause chest infiltrates. The disease is also known to result in psychomotor developmental impairment in long-term. Recent research has highlighted the role of *C. parvum* in colorectal cancer and other cancers of the digestive tract in immunocompromised individuals.

DIAGNOSIS

Infection is detected by microscopic examination of stool using modified acid-fast staining wherein the oocysts appear as small, spherical bodies (2–6 µm). A minimum load of 500,000 cysts per mL is required to detect it by acid-fast staining. At least three stool samples should be examined as shedding of oocysts is intermittent. Moreover, due to the small size of oocysts, they may be missed or may be reported as contaminants in the stool samples. Modified staining methods like fluorescent stain (auramine O) or immunofluorescent stains are more specific stains which improve detection rate.

Detection of *Cryptosporidium* spp. by oocyst antigen capture using ELISA improves the chances of isolation from the stool samples. Newer molecular methods used for detection include PCR, immunofluorescence microscopy, colorimetric in situ hybridization, fluorescent in situ hybridization, and real time quantitative PCR. The applicability of these methods is still in research settings. Biopsy of the intestine may reveal *Cryptosporidium* organisms in the microvillus border especially in the jejunum. Histopathology of the intestine reveals villus atrophy, epithelial flattening and inflammation of the lamina propria.

TREATMENT

The mainstay of treatment is adequate rehydration. Nitazoxanide is the only FDA approved drug for use in cryptosporidiosis. It is to be given for 3 days duration at the following dose—1–3 years: 100

mg BD, PO; 4–11 years: 200 mg BD, PO; and ≥ 12 years: 500 mg BD, PO. The drug is not licensed for use in infants. It is available both in tablet and suspension form. Certain drugs like thymidylate synthase inhibitors (5-fluorouracil) have also shown promising results in research settings. Agents under evaluation for chemoprophylaxis of cryptosporidiosis in children with HIV infection include rifabutin, clarithromycin and hyperimmune bovine colostrums. Research is still ongoing for production of a suitable vaccine.

The most effective strategy for infection containment remains provision of hygienic potable water supply and effective and safe water storage, sanitation and sewage management.

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IN A NUTSHELL

1. *Cryptosporidium* is the emerging causative agent of acute diarrhea in young children.
2. Infection is transmitted through contaminated water, and acquired by fecal-oral route.
3. Watery diarrhea is the main clinical presentation. In malnourished children, *Cryptosporidium* frequently causes persistent diarrhea.
4. Nitazoxanide (given for 3 days) is the drug of choice for acute infections.

Chapter 32.7

Ascariasis

Sutapa Ganguly

PHYLUM: NEMATHELMINTHES; CLASS: NEMATODA; GENUS: ASCARIS LINNAEUS; SPECIES: ASCARIS LUMBRICOIDES

Ascaris lumbricoides is the giant roundworm of the humans, responsible for ascariasis in humans. It has a worldwide distribution, being more prevalent in tropical countries such as India, China and South-East Asia. About 25% of the population in these areas is found to be infested with *A. lumbricoides*. The annual global mortality is as high as 20,000, mainly due to intestinal complications and morbidity is 10,00,000 cases mainly due to malnutrition and pulmonary complication. Ascariasis occurs in persons with unhygienic habits.

MORPHOLOGY

The Worm

The adult worm has resemblance to earthworm and is light brown or pink in color when fresh from intestine, but it gradually changes to white. Males are 2–4 mm in diameter and 15–31 cm long. The tail end of the male is curved ventrally in the form of a hook having a conical tip. Females are 3–6 mm in diameter and 20–49 cm long. The worm tapers at both ends, the anterior end being thinner than posterior. The egg-laying capacity of the female *Ascaris* is enormous liberating about 200,000 eggs daily. The digestive and reproductive system floats inside the body cavity containing an irritating fluid. The irritant action is due to the presence of a substance *ascaron* which is protease in nature. The allergic manifestation seen in the infected individuals is due to this ascaron. The adult worm lives in the jejunum and maintains its position against intestinal peristalsis by its muscle tone. It can live in the human host for 12–18 months.

Egg

The eggs liberated by a fertilized female pass out with feces of the human host. The *fertilized egg* is round or oval, 60–70 µm in

length and 40–50 µm in breadth, and golden brown due to bile staining (**Fig. 1A**). It is surrounded by a thick smooth translucent albuminous shell thrown into mammillations. Inside is a large conspicuous unsegmented ovum. There is a clear crescentic area at each pole. It floats in saturated solution of common salt. The female even if not fertilized, is capable of liberating eggs. The *unfertilized eggs* are narrower, longer and more elliptical; they are brownish, have a thinner shell with an atrophied egg inside (**Fig. 1B**). They do not float in salt solution, being heaviest of all helminthic eggs. Both fertilized and unfertilized eggs may be present in the stool. Presence of only unfertilized eggs signifies that the host is harboring female *Ascaris* or mating between males and females has not occurred.

LIFE CYCLE

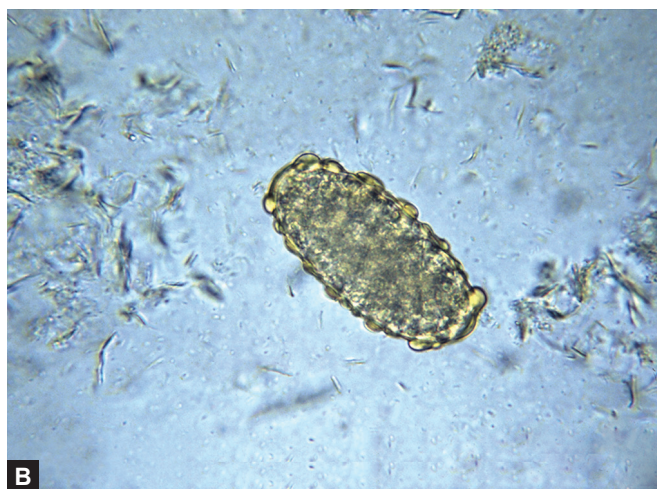
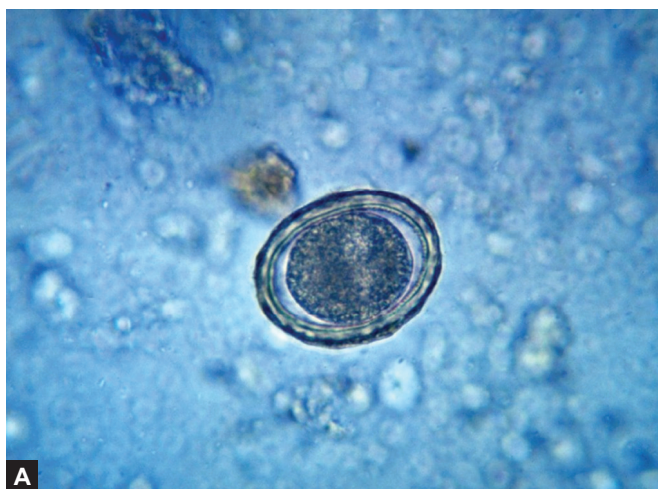
The worm passes its life cycle in one host and no intermediate host is required. Continuance of the species is maintained by transfer from one individual to another. Man is the only known definitive host of *A. lumbricoides*. The unsegmented, fertilized ovum passed in the stool takes 10–40 days in the soil, depending on the atmospheric temperature and humidity to develop into the mature and infective state. Infections in humans occur when this fertilized egg containing the rhabditiform larva is ingested with food, drink or raw vegetables. Embryonated eggs pass down into the duodenum where the digestive juices weaken the egg shell and stimulate the enclosed larvae into activity. It penetrates the duodenum and enters the blood stream. From there it is carried to the liver and heart, enters the pulmonary circulation to break free into the alveoli, where it grows and moults twice. In 3 weeks the larvae pass from the respiratory system to be coughed and swallowed and thus returned to the small intestine where they moult once and mature into adult male and female worms in 6–10 weeks. The gravid females begin to discharge eggs into the stool about 2 months from the time of infection. The cycle is again repeated (**Fig. 2**).

CLINICAL FEATURES

The adult worm inhabits the upper part of small intestine, thus symptoms are mainly gastrointestinal.

Nutritional Deprivation

The parasite consumes huge amount of calories as they have to thrive against the peristaltic movement of the jejunum. They imbibe the



Figures 1A and B This micrograph reveals (A) fertilized egg of the round worm *Ascaris lumbricoides*; 400x. Fertilized eggs are rounded, have a thick shell; (B) unfertilized egg; it is elongated and larger, thinner shelled, covered by a more visible mammillated layer, sometimes covered by protuberances

Source: CDC/Dr Mae Melvin; Public Health Image Library (PHIL), CDC, USA.

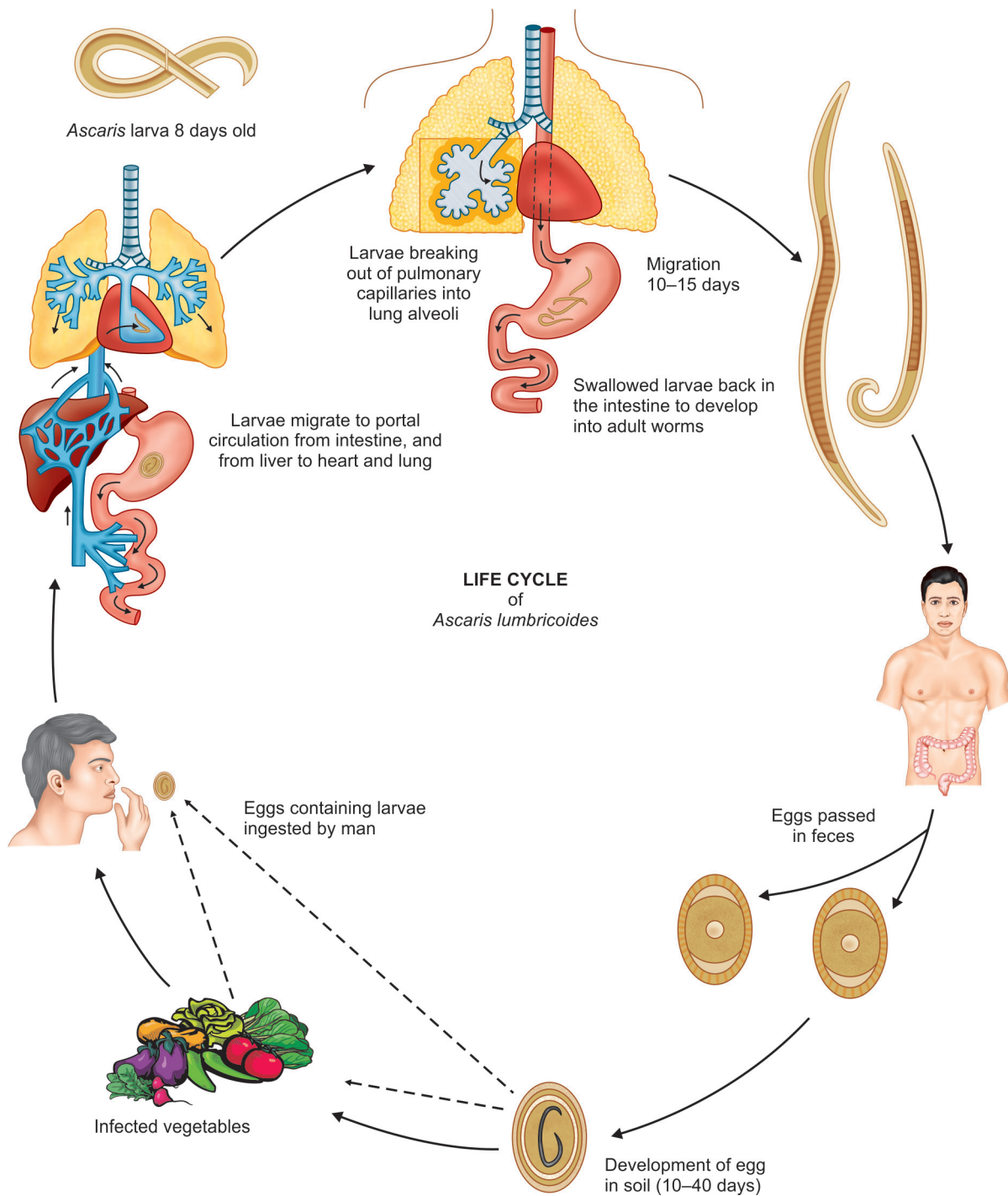


Figure 2 Life cycle of *Ascaris*

nutrition from the host who may suffer from protein energy malnutrition in case of heavy infestation. *Ascaris* infection is frequently associated with symptoms and signs of vitamin A deficiency.

Mechanical Effects

Heavy *A. lumbricoides* infestations may cause acute intestinal obstruction due to a ball of worms. It may also result in intussusception. The adult worm may penetrate through the ulcers of the alimentary tract. Children may present with vomiting, abdominal distension and cramps.

Ectopic Ascariases

The worms frequently migrate and may enter the stomach and may be vomited out or may pass up through the esophagus at night, coming out through the nose and mouth. During migration it may enter the glottis, causing laryngospasm and death due to suffocation. Wandering *Ascaris* may enter the lumen of appendix causing appendicitis. Obstructive jaundice and hemorrhagic pancreatitis may occur when the worm enters the biliary passage and/or the pancreatic duct. At times it may penetrate high up in the liver causing liver abscesses.

Allergic Symptoms

Larvae migrating through the tissues may cause allergic symptoms, fever, urticaria and granulomatous disease. It may present as Loeffler syndrome, characterized by fever, cough, dyspnea, pulmonary infiltrates and blood eosinophilia. Larvae may be observed in sputum.

LABORATORY DIAGNOSIS

Direct Evidence

The adult worms may pass out spontaneously with stool or per anum in between the stool (**Fig. 3**). They may be vomited out or pass through the nares. Administration of anthelmintic may lead to expulsion of worms and its detection. Direct microscopic examination of the saline emulsion of stool reveals fertilized and unfertilized eggs. Concentration by floatation method may increase the probability of detections of eggs in the stool. Barium imaging may detect adult worms which ingest the barium within 4 to 6 hours (string like shadows). Ultrasound can detect worms in pancreaticobiliary ducts.

Indirect Evidence

Eosinophilia is present during early stages of invasion. If present in the later stages, suggest associated strongyloidiasis or toxocariasis infection.



Figure 3 A mass of *Ascaris lumbricoides* worms, passed by a child in Kenya, Africa

Source: James Gathany; Public Health Image Library (PHIL), CDC, USA.

TREATMENT

Anthelmintic drugs should be given to the child as well as family members. Albendazole (single dose 400 mg in children aged 2 years and above; and 200 mg in younger children) is the drug of choice. Alternative drugs include pyrantel pamoate (single dose 10 mg/kg to maximum one gram), mebendazole (100 mg twice daily for three days), nitazoxanide, and ivermectin (150–200 mcg/kg single dose).

PREVENTION

Prevention of ascariasis requires hygienic habits and effective fecal treatment systems. This is particularly true for ascariasis as eggs are difficult to kill (they commonly survive 1–3 years). The eggs may get onto vegetables when improperly processed human feces from infected persons are used as fertilizers for food crops. Thus, fruit and vegetables should be washed thoroughly before consumption. Bleach does not easily kill *Ascaris* eggs but removes the sticky film which allows the eggs to be rinsed away.

IN A NUTSHELL

1. *Ascaris lumbricoides* is the giant roundworm of the humans, responsible for ascariasis in humans. It has a worldwide distribution.
2. The adult worm inhabits the upper part of small intestine, thus symptoms are mainly gastrointestinal.
3. Albendazole is the drug of choice. Alternative drugs include pyrantel pamoate, mebendazole, nitazoxanide, and ivermectin.

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Chapter 32.8

Hookworm Infestation

Maitreyi Basu, Sutapa Ganguly

PHYLUM: NEMATODA;

FAMILY: ANCYLOSTOMATIDAE;

GENUS: NECATOR/ANCYLOSTOMA;

SPECIES; N. AMERICANUS, A. DUODENALE

Hookworm infestation is an important cause of iron deficiency anemia in the developing countries. Hookworm, a parasitic nematode, lives in the intestine of human host. Two species of hookworms usually infest the humans, namely *Ancylostoma duodenale* and *Necator americanus*. While *A. duodenale* predominates in the Middle East, India and North Africa Western Australia, *N. americanus* infests people in Americas, Sub Saharan Africa, South East Asia, Southern China and Indonesia. Other species of hookworm are zoonotic and include *A. celyanicum*, *A. caninum* and *A. braziliense*. Dog hookworm *A. caninum* can cause eosinophilic enteritis syndrome in humans. *A. braziliense*, a parasite in dogs and cats causes cutaneous larva migrans in humans by its larval stage.

EPIDEMIOLOGY

Hookworm affects more than 500 million people globally. Soil, moisture and warmth are necessary for the parasite to thrive and hence, it is prevalent in rural areas with poor sanitary conditions. Hookworm infestation is associated with economic

underdevelopment and poverty. High rates of infection are seen among agricultural workers and tea garden laborers. People of both sex and all ages are susceptible. *A. duodenale*, also called *Old world hookworm* can withstand harsher climatic conditions. Among Asian countries, it predominates in Northern India, mainly Punjab and Uttar Pradesh, also Sri Lanka and Northern China. *N. americanus*, though called American or *New world hookworm*, has spread to Asian countries and is common in parts of India other than Punjab and UP, Sri Lanka, Southern China and South East Asia.

LIFE CYCLE

Man is the definitive host of hookworm and harbor the adult worms. Multiplication of the worm does not occur inside man. No intermediate host is required for the spread of infection. The eggs containing segmented ova passes through human feces to soil. In 8–10 days, each egg first develops into a rhabditiform larva, 250 µm long, which moults twice to form the infective filariform larva, measuring 500–600 µm in length. The infective larval stage of hookworm remains in a developmentally arrested state in warm and moist soil. Human infection occurs as *A. duodenale* and *N. americanus* larva penetrate skin when man walks barefoot over feces contaminated soil. In gardeners and miners, the skin of the hands may be the portal of entry. *A. duodenale* larva can also infect humans when ingested. Following entry in man, the larva in subcutaneous tissues undergoes extraintestinal migration. They enter into the lymphatics or small venules to reach right heart. From pulmonary circulation, they break into alveoli, migrate upwards through air passages to pharynx and swallowed. Orally ingested larva may develop in intestine. The larva travels the GI tract and settles in small intestine where they develop into adult worms after moulting twice (**Fig. 1**).

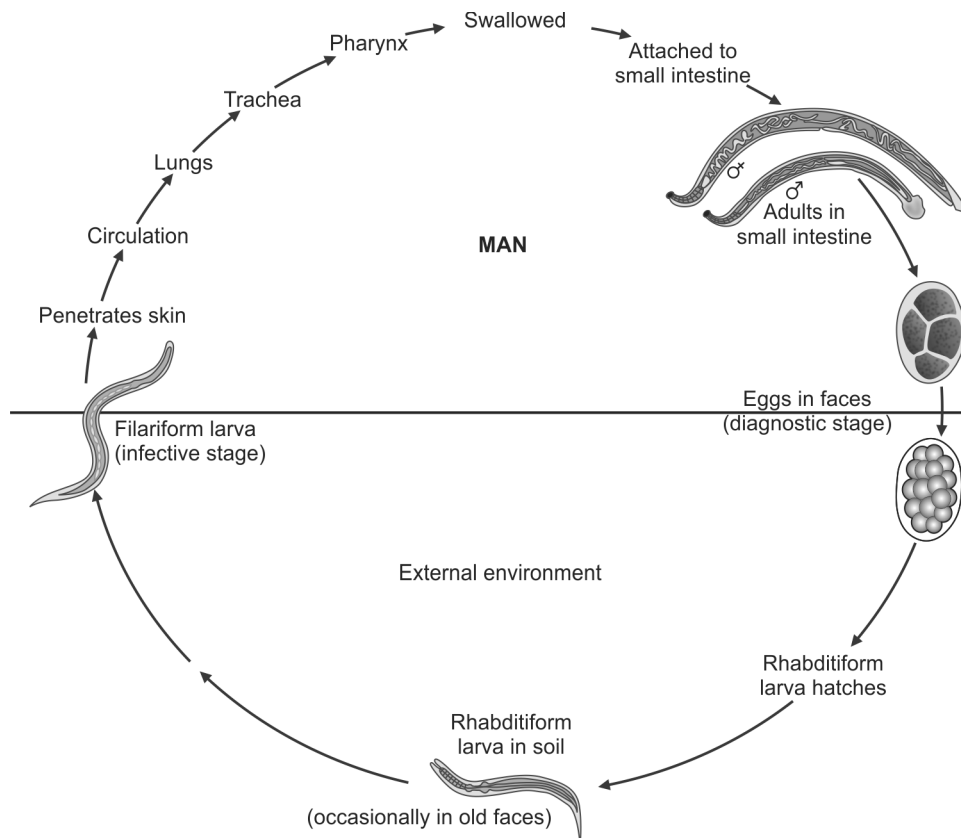


Figure 1 Life cycle of hookworms: *Ancylostoma duodenale* and *Necator americanus*
Source: Public Health Image Library (PHIL), CDC, USA.

The male and female adult worms measure 5–13 mm in length. The buccal capsules of adult *N. americanus* have cutting plates, whereas that of *A. duodenale* has teeth to secure intestinal attachment. The extraintestinal migration and development into adult worms may take 2 months, though *A. duodenale* larva may remain developmentally arrested inside human body for many months. Mature worms can lay eggs up to 10,000–30,000/day. In the intestine, the eggs are laid in an unsegmented stage. During passage through intestine segmentation proceeds up to 4-celled stage (**Fig. 2**). The eggs when passed out in feces are not infective to man.

Translactational transmission of *A. duodenale* larva has been described. The larva may not undergo passage through lungs, remain dormant in muscles and after childbirth reach mammary gland through circulation and infect infants through mother's milk.

PATHOGENESIS

The main consequence of hookworm infestation is iron deficiency anemia due to intestinal blood loss. Heaviest parasite load occurs in children. The adult hookworms attach themselves to the mucosa and submucosa of small intestine with their teeth or cutting plates and remain there with negative suction pressure in the buccal capsules. The worm secretes anti-inflammatory substance to minimize host inflammation at the site of attachment. Capillaries in lamina propria rupture, the worm ingest blood, which is anticoagulated and lysed to release hemoglobin that is digested. Anemia is caused by withdrawal of blood by the parasites and chronic hemorrhage from the puncture sites. *A. duodenale* can draw 0.2 mL blood/day, while *N. americanus* draws 0.03 mL blood/day. It is estimated that loss of hemoglobin for each 12 worms is about 1%. This iron loss cannot be compensated in nutritional deficient individuals. Also, hypoalbuminemia may develop leading to anasarca.

CLINICAL FEATURES

There are no specific signs and symptoms of hookworm infection. Dyspeptic troubles and epigastric discomfort may occur. Symptoms are related to the complications of heavy infections causing iron/protein deficiency. Iron deficient anemia and protein malnutrition occur. Iron deficiency can lead to abnormal appetite showing a perverted taste for things like mud, lime (pica). Prolonged iron deficiency cause physical growth retardation and intellectual defects. Early intestinal infection is associated with eosinophilia. Children with chronic hookworm infection acquire a yellow-green pallor called chlorosis. During migration of *A. duodenale* and *N.*

americanus larva through lungs, laryngotracheobronchitis and pharyngitis can occur giving rise to cough. Eosinophilic enteritis by *A. caninum* cause epigastric pain that increases with food intake and radiate outward. It may simulate appendicitis. An infantile form of ancylostomiasis has been described. There is severe anemia, diarrhea, and melena that may be life-threatening.

Skin Lesions

Ankylostoma dermatitis or ground itch occurs at the site of entry of larva in the skin. There is vesiculation and local edema at the site of entry of larva. It is more common with *Necator* than *Ancylostoma* and persists for 1–2 weeks. This precedes ancylostomiasis by 2–4 months. Creeping eruption or cutaneous larva migrans is a condition when the filariform larva migrates through the skin for months to 2 years and produces a reddish itchy papule along the path of migration. They migrate forming a serpiginous tunnel with roof being formed by stratum granulosum and floor by the corium. This manifest more with *A. braziliense* and *A. caninum* infection, though rarely reported with *N. americanus* larva.

DIFFERENTIAL DIAGNOSIS

Hookworm anemia should be differentiated from other causes of anemia, e.g., nutritional anemia, other causes of iron deficiency anemia and chronic gastrointestinal blood loss especially ulcerative disorders, and diverticulum. Creeping eruption in skin can also occur due to migrating *Strongyloides* larva (larva currens). Complications of tissue migration happen more frequently with roundworm giving rise to similar symptoms. However, intestinal obstruction caused by roundworm is not observed with hookworm infection.

DIAGNOSIS

Macroscopic examination of stool may show adult worms. Microscopic examination of stool helps more in identifying characteristic hookworm eggs. The eggs in stool are colorless, float-in saturated solution of common salt and contain a segmented ovum with four blastomeres. Quantitative methods are available like egg counting in stool to detect heavy worm burden. However, *A. duodenale* and *N. americanus* eggs are indistinguishable. Species can be identified by egg hatching and examination of third stage larva or by examination of mature adult worms. In eosinophilic enteritis caused by *A. caninum*, eggs are not detected in stool. Colonoscopy is done to document intestinal ulcerations; blood shows eosinophilia.

Indirect Evidence

Blood examination reveal microcytic hypochromic anemia; at times dimorphic anemia can occur. Eosinophilia is associated with early enteritis. Stool examination for occult blood is positive. Charcot-Leyden crystals are often found in stool.

MANAGEMENT

Specific treatment consists of deworming with anthelmintic drugs. Albendazole 400 mg per orally in single dose achieves high cure rates. *N. americanus* hookworms may require additional doses for eradication. Albendazole is effective against intestinal stage and also when the worm is migrating under the skin. Mebendazole 100 mg twice daily for 3 days is also effective. Mebendazole can be used in *A. caninum* enteritis. Benzimidazoles (albendazole, mebendazole) are not recommended for treatment of pregnant women in the first trimester due to their potential embryotoxic and teratogenic effect. WHO currently recommends benzimidazole drugs for more than 1 year age. In children 1–2 years of age, 200 mg of albendazole is enough to avoid toxicity. Pyrantel palmoate 11 mg/kg once daily for 3 days is a good alternative. Supportive management includes oral iron replacement. Correction of other protein nutrient deficiencies should be done as needed.

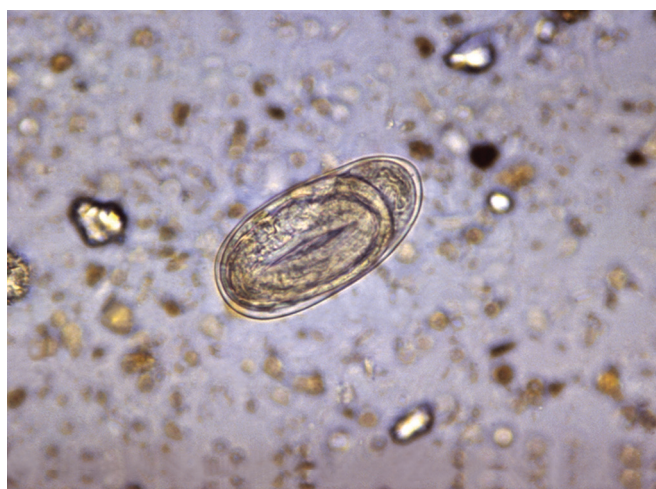


Figure 2 This embryonated egg is indistinguishable between the *Ancylostoma duodenale* or *Necator americanus* hookworm. Note the thin shell, oval or ellipsoidal shape

Source: Public Health Image Library (PHIL), CDC, USA.

PREVENTION

Prevention of hookworm infestation requires good sanitation measures and personal hygiene. Avoidance of walking barefoot over soil and use of night soil as fertilizer may minimize infection. Deworming of pet dogs is also important in this context.

IN A NUTSHELL

1. Hookworm lives in the intestine of human host. Two species of hookworms usually infest the humans, namely *Ancylostoma duodenale* and *Necator americanus*.
2. Hookworm infestation is an important cause of iron deficiency anemia in the developing countries.
3. It also cause creeping eruption or cutaneous larva migrans where the filariform larva migrates through the skin for months to 2 years and produces a reddish itchy papule along the path of migration.
4. Albendazole achieves high cure rates.

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Chapter 32.9

Trichuriasis

Sutapa Ganguly

PHYLUM: NEMATODA;**FAMILY: TRICHURIDAE;****GENUS: TRICHURIS;****SPECIES: TRICHURIS TRICHIURA**

Trichuris trichiura, commonly known as the whipworm, resides in the cecum, ascending colon, and appendix. It is distributed worldwide with an estimated 1 billion infections. It is common in warm moist conditions, especially in Asia and to a lesser degree in Africa and South America.

MORPHOLOGY**Adult Worm**

The worm resembles a whip, the anterior three fifth is very thin and hair like and consists of a long esophagus. The thicker posterior portion contains intestine and sex organs. They attach to the host through their slender anterior end and feed on tissue secretions instead of blood. Females are larger than the males, approximately 30–45 mm. The posterior end of females is bluntly round compared to their male counterparts with a coded posterior end. The adult worm may live in the intestine for many years.

Eggs

Trichuris eggs are barrel shaped, brown (bile stained), about 50 X 25 µm. It has a double shell, the outer shell being bile stained. The eggs contain unsegmented ovum when they leave the human host. They float in saturated solution of common salt. The eggs when freshly passed are not infective to man.

LIFE CYCLE

No intermediate host is required. The worm passes the life cycle in one host, man. A change of host is necessary for the continuation of the species. The eggs come out of the human host with feces and the development proceeds in the damp earth or in water. In tropics the rhabditiform larva develops within the eggs in the course of 3–4 weeks. In temperate climates the larva takes a long time (6–12 months) to develop. The embryonated eggs are infective to man. Man is infected when the embryonated eggs are swallowed with food and water. The egg-shell is dissolved by the digestive juices and the larva emerges through one of the poles of the eggs. The liberated larvae pass down into the cecum, their site of localization. They grow directly into the adult worm and embed their anterior parts in the mucosa of the intestine. The worms become sensually mature within a month and the gravid female begins to lay eggs. The female *T. trichiura* lays 2,000–10,000 single celled eggs per day. The cycle is then repeated (Fig. 1).

CLINICAL FEATURES

Incubation period is 60 days. Infection is asymptomatic in most cases. In heavy infections the patient often complains of abdominal pain, mucous diarrhea often with blood streaked stool and loss of weight. Worms inhabiting the vermiform appendix may give rise to symptoms of acute appendicitis. Prolapse of rectum has occasionally been observed in massive trichuriasis.

MANAGEMENT AND CONTROL**Laboratory Diagnosis**

Microscopic examination of a saline emulsion of stool will reveal characteristic barrel shaped eggs (Fig. 2). Adult worms may occasionally be present in the stool. The degree of infection can be determined by the egg count.

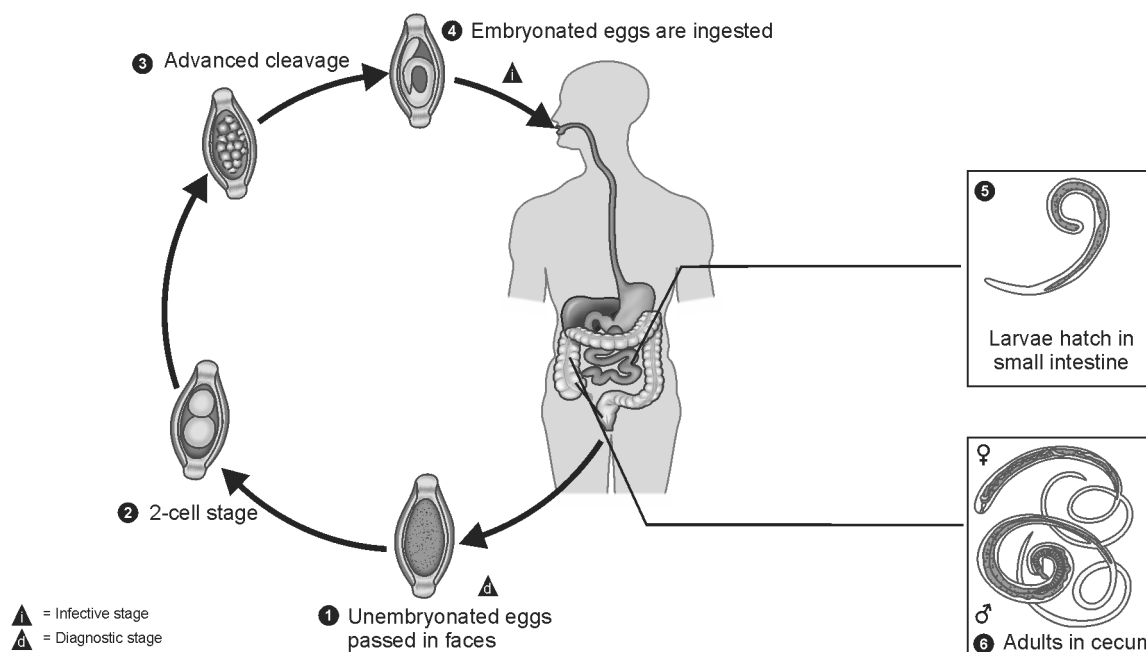


Figure 1 Life cycle of *Trichuris trichiura*, the causal agent of Trichuriasis
 Source: Public Health Image Library (PHIL), CDC, USA.

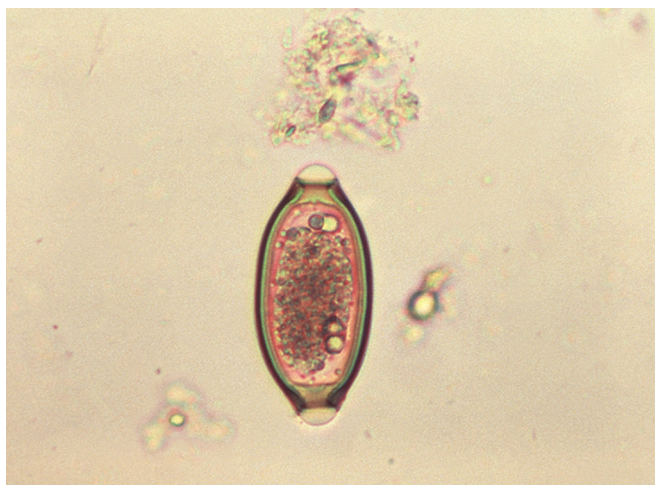


Figure 2 Egg from the “human whipworm”, *Trichuris trichiura*
 Source: CDC/BG Partin. Public Health Image Library (PHIL), CDC, USA.

Treatment

Thiabendazole or mebendazole (100 mg twice daily for 3 days) may be used in the treatment of trichuriasis. Albendazole (400 mg daily for 3 consecutive days) is also effective. Ivermectin 200 µg/kg is also used in combination with albendazole (400 mg).

Prophylaxis

Proper disposal of stool, hand washing, prevention of consumption of uncooked vegetables and fruits grown in native gardens help to prevent trichuriasis.

IN A NUTSHELL

1. *Trichuris trichiura* commonly known as the whipworm, resides in the cecum, ascending colon, and appendix.
2. Infection is asymptomatic in most cases. In heavy infections the patient often complains of abdominal pain, mucous diarrhea often with blood streaked stool and loss of weight.
3. Thiabendazole, mebendazole, or albendazole may be used for the treatment of trichuriasis.

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Chapter 32.10

Enterobiasis

Dhrubojoyoti Mridha, Sutapa Ganguly

PHYLUM: NEMATODA;
FAMILY: OXYURIDAE;
SPECIES: *E. VERMICULARIS*

Enterobius vermicularis, also known as pinworm or threadworm is a small nematode (1 cm) that mainly presents with perianal itching. High prevalence of infection is reported from South Asia (39% in Thailand) and India (61%). Prevalence of infection is highest in children 5–14 years of age.

LIFE CYCLE

No intermediate host is required. Each of the eggs, newly laid in perianal skin, containing larva completes its development in 24–36 hour in the presence of oxygen. Infection occurs with ingestion of these eggs (**Fig. 1**). The egg shells are dissolved by the digestive juices and larvae escape in the small intestine where they develop into adolescent worm. After the worm become sexually mature male fertilizes the female and dies. The gravid female then migrates from the small intestine down to the cecum and colon (and also the vermiform appendix) (**Fig. 2**) and resides there until eggs develop. The female then wanders down the rectum and comes out of the anal opening

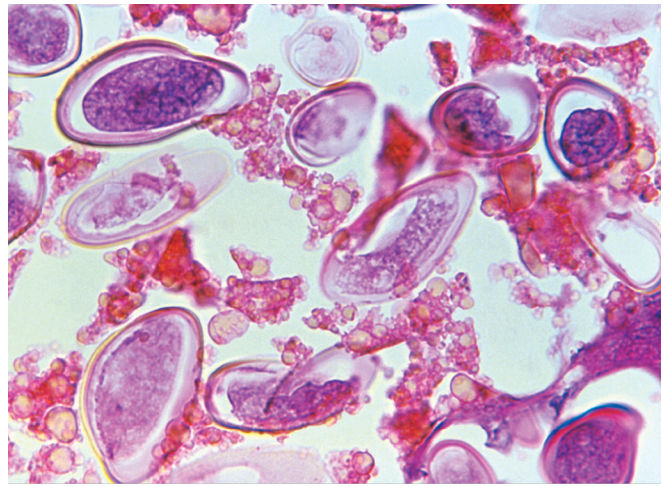


Figure 2 Section of appendiceal tissue with presence of pinworms, *Enterobius vermicularis*

Source: CDC/Dr George R Heal; Public Health Image Library (PHIL), CDC, USA.

during the night to deposit the eggs in perianal skin. The whole cycle is completed in 2–8 week time. Persons handling the night cloths and bed linens of infected persons often contract the infection.

Both male and female are white in color. Adult male measures 2–4 mm in length and 0.1–0.2 mm across its girth. Posterior third

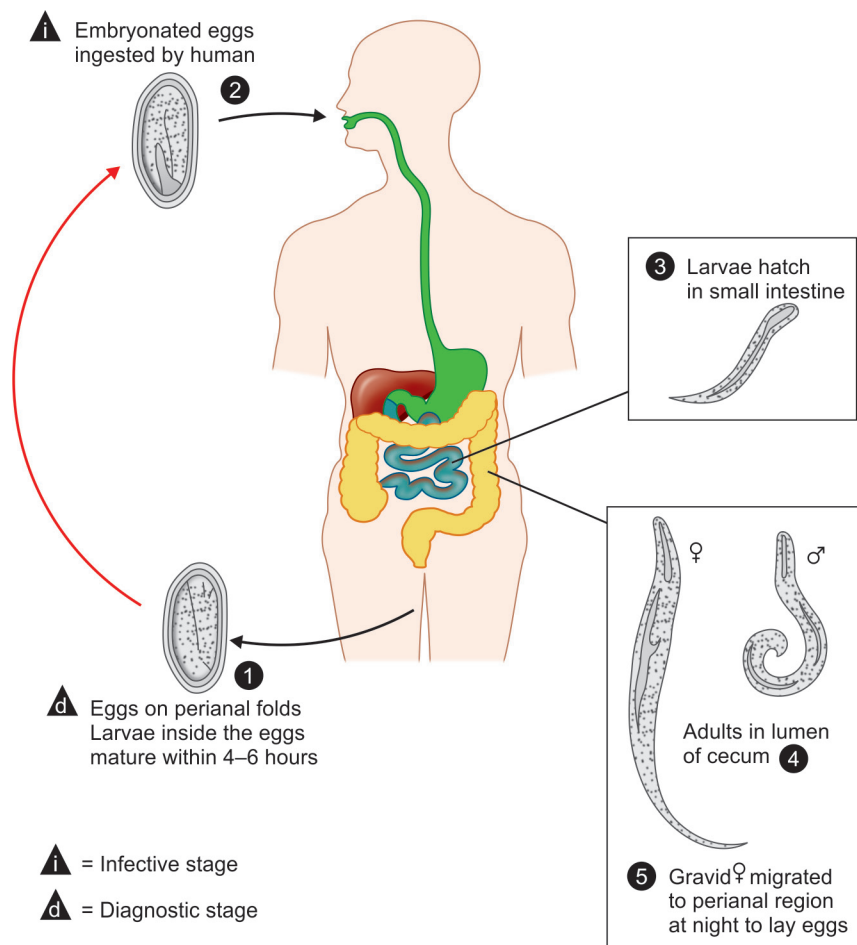


Figure 1 Life cycle of *Enterobius*

of the body is curved and sharply truncated. It is rarely seen except after a purge because it usually dies after fertilizing the female. Adult female measures 8–12 mm in length and 0.3–0.5 mm across its thickest part. The number of eggs in a gravid female pinworm range from about 11,000 to 16,000.

TRANSMISSION

Pinworms spread through human-to-human transmission, by ingesting (i.e., swallowing) infectious pinworm eggs. Eggs do not tolerate heat well, but can remain infectious in moist and low temperatures for up to 3 weeks. As freshly laid eggs are sticky, they are easily transmitted from perianal region to fingernails, hands, night-clothing, bed linen, toys, bathroom fixtures, food, and furs of household pets, water and other objects. Shaking out bed clothes and linen frequently makes the tiny eggs airborne which when gets inhaled and be swallowed later initiates infection. Some of the hatched pinworm larvae enter the gastrointestinal tract of the original host by upward migration from perianal region which is known as *retroinfection*; it leads to a heavy parasitic load and ensures that the pinworm infestation continues.

Eggs get deposited in fingertip when children put their finger in perianal area for scratching which, when kept inside mouth initiates life cycle of worm (*autoinfection*). As children have inherent tendency to put their finger inside mouth and other members of the family are often infected, persistence of infection and reinfection after treatment is very common in children.

CLINICAL FEATURES

Most common symptom is perianal pruritus. Other manifestations include cellulitis, granuloma or abscess in the perianal area resulting from scratching due to intense itching. Girls may develop vaginitis and urinary tract infection. Complications include chronic salpingitis, hepatitis, pelvic inflammatory disease, and peritonitis from aberrant migration of worms. Eosinophilic ileocolitis is rare.

DIAGNOSIS

Finding the female worm or the eggs confirms the diagnosis of pinworms. At night, the adult worms can sometimes be seen directly around the anal area or in pajamas. The worm (one-quarter to one-half inch long) should be removed and preserved in 75% ethyl alcohol until microscopic examination. If adult worms are not visible, conduct a tape test in the morning. Apply a piece of transparent adhesive tape against the folds of skin around the anus to pick up any eggs or worms. Seal in a plastic bag and send for microscopic examination. Repeated examination increases the chance of detecting ova which is plano-convex, and not bile stained, surrounded by a transparent shell, contains a tadpole like larva and floats in saturated solution of common salt.

Pinworms are rarely spotted in stool samples. Because bathing or a bowel movement can remove the eggs, the tape test should be done as soon as the person wakes up in the morning. Enterobiasis

need to be differentiated from Crohn disease, hidradenitis suppurativa, proctitis, anusitis, and ulcerative colitis.

TREATMENT AND PREVENTION

Pinworm infection can be cured. Anthelmintic drug should be given to infected child as well as family members. Drug of choice is single oral dose of albendazole (400 mg), mebendazole (200 mg) or pyrantel pamoate (11 mg/kg); dose to be repeated after 14 days. It is important to take appropriate care and maintain hygiene to prevent autoinfection. Morning bath and frequent change of underclothing should be encouraged. Washing of bed cloth, bed sheet twice a week decreases risk of autoinfection. Keep fingernails short and clean. Discourage nail biting. Clean toilet seats daily. Wash hand before meal and after using toilet.

IN A NUTSHELL

1. Enterobiasis is caused by a pinworm that mainly affects children 5–15 years.
2. Infection is acquired through ingestion of eggs. Autoinfection causes worm to inhabit the same host indefinitely. Retroinfection is also common and clinically significant.
3. Most common symptom is perianal pruritus. Pinworm infection should be kept in mind in a girl with vaginal pruritus or urinary tract infection.
4. Stool examination is not helpful for diagnosis. Repeated microscopy of adhesive tapes that has been applied to the perianal area early in the morning before bath, increases chance of detection of pinworm ova.
5. As none of the anthelmintics is effective against eggs, two doses of albendazole/mebendazole/pyrantel pamoate are advised, 14 days apart.

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Chapter 32.11

Strongyloidiasis

Ravi Ambey, Tripty Naik

Strongyloidiasis is a chronic parasitic infection of humans caused by soil transmitted helminths, *Strongyloides stercoralis*. In malnourished children, strongyloidiasis remains an important cause of chronic diarrhea, cachexia and failure to thrive. Without appropriate therapy, the infection does not resolve and may persist for life. It has the potential for severe and life-threatening infection in cases of immunodeficiency (hematologic malignancies and immunosuppression) with 60–90% mortality rate. The infection is most common in tropical and subtropical countries with nearly 30–100 million people being infected worldwide. Precise data are unknown as the infection is mostly asymptomatic and the diagnostic methods lack sensitivity.

ETIOLOGY

Strongyloidiasis is caused by nematode or roundworm of genus *Strongyloides*. Of the 40 species, *S. stercoralis* mainly causes disease in human. The free-living larvae enter the body through exposed skin such as barefoot, contact with human waste or sewage. Like other soil-transmitted helminthiasis the risk of infection is associated with hygiene, making children especially vulnerable

to infection. There have been rare cases of person-to-person transmission in organ transplantation.

PATHOGENESIS

The life cycle of *S. stercoralis* (Fig. 1) has two stages: (i) a free-living life cycle (rhabditiform larvae) and (ii) a parasitic life cycle (filariform infective larvae) with three developmental forms: (i) adult, (ii) rhabditiform larva and (iii) filariform larva. The infective filariform larva presents in soil enters the body through skin, enters blood stream and reaches lungs. It traverses the tracheobronchial tree and is swallowed in gastrointestinal tract. In intestine, it develops into adult female and passes egg. The eggs instead of passing in feces hatch in intestine as rhabditiform larvae. Larvae develop into infective filariform larvae which reinfect the host by invading intestine or the skin of perineum, buttocks and thighs. This is known as *autoinfection* and is unique for *Strongyloides* infection. Alternatively, the rhabditiform larvae hatched from the eggs pass with feces into the soil. Symptoms result when larva migrates through various tissues of body. Impaired host defense and repeated autoinfection cause hyperinfection syndrome and larvae to disseminate throughout body. The risk factors for hyperinfection or disseminated disease are summarized in **Box 1**. Human T-cell lymphotropic virus type 1 (HTLV-1) infection has a bidirectional relationship with *Strongyloides*; coinfection with *Strongyloides* shortens the preleukemic phase of HTLV-1 infection; the *Strongyloides* antigen accelerates leukemogenesis, and treatment of the *Strongyloides* infection may actually decrease HTLV-1 viral load.

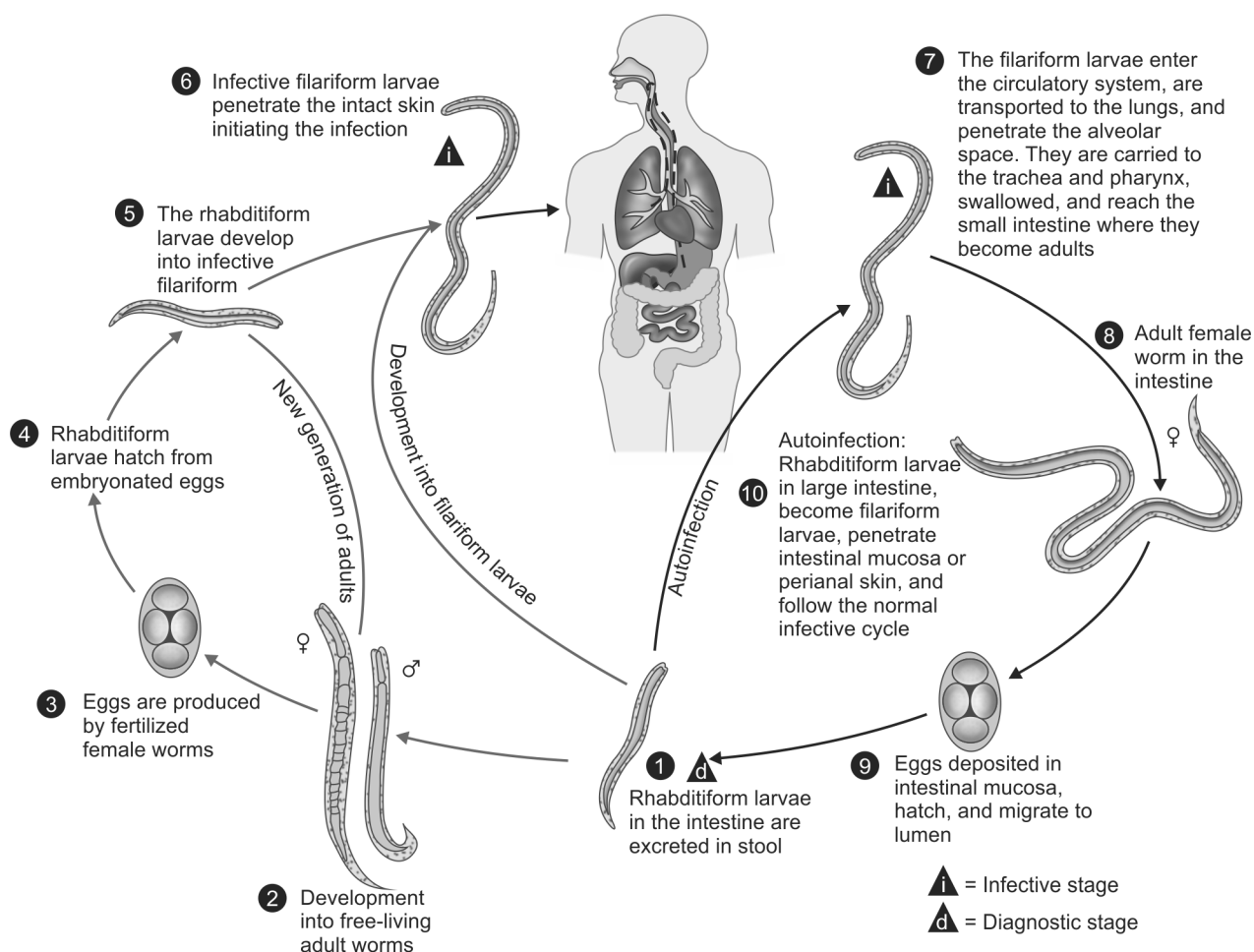


Figure 1 Life cycle of *Strongyloides stercoralis*

Source: Public Health Image Library (PHIL), CDC, USA (Content provider: CDC/Alexander J da Silva, Ph D/Melanie Moser, 2002)

BOX 1 Risk factors for hyperinfection or disseminated disease with *Strongyloides*

- Alcoholism
- Chronic renal failure and end-stage renal disease (ESRD)
- Diabetes mellitus
- HIV/AIDS
- Human T-cell lymphotropic virus type 1 (HTLV-1) infection
- Hypogammaglobulinemia
- Malignancy or neoplasm, particularly hematologic malignancies (lymphoma, leukemia)
- Malnutrition
- On treatment with corticosteroids or other immunosuppressives
- Solid organ and bone marrow transplant

CLINICAL FEATURES

Most infections with strongyloidiasis are asymptomatic. Acute infection may cause rash, petechiae and itch at the site of entry of parasite. Symptoms, if present, are mostly nonspecific respiratory and gastrointestinal in the form of cough, tracheal irritation, wheeze, abdominal pain, abdominal fullness, diarrhea and constipation. Many times infection may remain undiagnosed for life. *Chronic infection* may cause growth failure, malabsorption, protein-losing enteropathy or may mimic asthma. Cutaneous symptoms include chronic urticaria and the pathognomonic larva currens—a recurrent serpiginous maculopapular or urticarial rash along the buttocks, perineum, and thighs due to repeated autoinfection. It has been described as advancing as rapidly as 10 cm/hour.

Strongyloides causes hyperinfection or disseminated disease in immunocompromised because of autoinfection and its unique ability to multiply indefinitely within intestinal wall of the host. Hyperinfection syndrome implies signs and symptoms due to increased larval migration. Increased number of larvae is detected in feces or sputum. Disseminated infection occurs when larvae migrate beyond organs of autoinfective cycle (lungs and gut).

COMPLICATIONS

Hyperinfection is characterized by exaggeration of the symptoms found in immunocompetent host and is limited to gastrointestinal and respiratory manifestations. Disseminated strongyloidiasis involves almost all systems of the body—cutaneous, gastrointestinal, respiratory and central nervous system. Frank bacteremia and septicemia (mainly Gram-negative sepsis) can occur due to introduction of gut flora through disrupted mucosal barrier into blood stream. Unawareness of the condition, nonspecific manifestations and low sensitivity laboratory tests cause significant delay in diagnosis and a mortality rate approaching 90%.

DIFFERENTIAL DIAGNOSIS

- *Recurrent asthma*: Nonresponse to bronchodilators and steroids and worsening course may suggest *Strongyloides* infection.
- *Acute respiratory distress syndrome*: Sputum examination leads to diagnosis.
- *Other intestinal infections* (amebiasis, bacterial colitis, shigellosis): Strongyloidiasis is diagnosed by demonstration of organism in stool specimen.
- *Inflammatory bowel disease*, especially ulcerative colitis: History of steroid therapy, chronic colitis refractory to conventional immune-modifying management and endoscopic finding of distal attenuation of the colitis are helpful clues to the diagnosis of strongyloidiasis.

- *Pneumonia* in immunocompromised (*Pneumocystis*, *Cryptococcus*, *Mycobacterium*): Strongyloidiasis diagnosed by presence of larvae in sputum.
- *Loeffler pneumonia* (eosinophilic infiltration of lungs): Strongyloidiasis is one of the causes of the disease.
- Peritonitis and abdominal sepsis.

DIAGNOSIS

Mild peripheral eosinophilia and elevated IgE levels are present in 75% of chronic infections. Multiple stool examinations to detect larva in direct stool smear examination is the gold standard for diagnosis of strongyloidiasis. Chronic strongyloidiasis has low larval load and intermittent larval excretion in stool, therefore a single stool examination fails to detect 70% cases (sensitivity only 30–50%). Sensitivity increases to almost 100% with examination of seven stool samples. Several fecal concentration techniques are used to increase larval detection rate in feces including direct smear of feces in saline—Lugol iodine stain, Baermann concentration and nutrient agar plate cultures (APC). Hyperinfection is easier to detect due to higher parasite load.

Duodenal fluid aspiration via endoscopy or string test increases detection rate. Larvae can also be detected in sputum, cerebrospinal fluid (CSF), bronchoalveolar lavage (BAL) and intestinal biopsy in case of dissemination. Enzyme-linked immunosorbent assay (ELISA) for IgG antibody to *Strongyloides* is more sensitive (88–95% in various studies) than stool examination. Unfortunately, the test is not easily available and has cross reactivity with other helminth infections (filariasis, ascariasis and schistosomiasis). A significant decrease in antibody titer after 6 months of therapy can be used as a marker of cure. Luciferase immunoprecipitation system (LIPS) has better sensitivity (99%) and specificity (100%) than ELISA and less cross reactivity with other filarial antigens. Various imaging techniques and endoscopy can be used to detect gastrointestinal complications.

MANAGEMENT

Treatment for strongyloidiasis is recommended for all infected persons, whether symptomatic or not, due to the risk of developing hyperinfection syndrome and/or disseminated strongyloidiasis. Treatment of strongyloidiasis as recommended by Centers for Disease Control and Prevention (CDC) is summarized in **Box 2**. Patients hospitalized with strongyloidiasis should be placed on contact precautions. In patients with positive stool examination for *Strongyloides* and persistent symptoms, follow-up stool exams should be performed 2–4 weeks after treatment to confirm clearance of infection. If recrudescence of larvae is observed, retreatment is indicated.

BOX 2 CDC guidelines for treating strongyloidiasis**Acute and Chronic Strongyloidiasis**

Ivermectin, in a single dose, 200 µg/kg orally for 1–2 days. Relative contraindications include persons weighing less than 15 kg and those with confirmed or suspected concomitant *Loa loa* infection.

OR

Albendazole, 400 mg orally twice a day for 7 days. Hypersensitivity to benzimidazole compounds is a relative contraindication. It can be used in children as young as 1-year-old.

Hyperinfection Syndrome or Disseminated Strongyloidiasis

Ivermectin, 200 µg/kg/day orally until stool and/or sputum exams are negative for parasites for 2 weeks. For patients unable to tolerate oral therapy (ileus, obstruction, malabsorption), rectal or subcutaneous route can be used. Stop or reduce immunosuppressive therapy if being administered.

OUTCOME

Strongyloides hyperinfection or dissemination has a mortality rate approaching 90%. This is due to delay in diagnosis because of lack of awareness of the condition, nonspecific disease manifestations, poor detection rate in stool smear, no availability of better diagnostic tests and also due to unavailability of ivermectin in some endemic countries and selection of improper first-line therapy due to lack of standardized treatment guidelines.

PREVENTION

Strongyloidiasis, like other soil transmitted infections, can be prevented by proper hygiene, avoiding barefoot, hand washing and avoiding use of sewage as fertilizer. Severe infection can be prevented by screening for and treating asymptomatic strongyloid infection in HTLV-1 and malignancy patients and prior to starting steroid or immunosuppressive therapy.

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IN A NUTSHELL

1. Strongyloidiasis is a potentially fatal disease transmitted due to unhygienic condition.
2. Strongyloid has the unique ability of autoinfection and reinfecting host causing the parasite to remain in the host for decades or even life unnoticed.
3. Infection is mostly asymptomatic in immunocompetent and symptoms if occur are nonspecific.
4. Immunosuppression (malignancies and steroid therapy) and HTLV-1 infection are the most important risk factor for hyperinfection or dissemination with mortality 65–90%.
5. Peripheral eosinophilia is seen in 65% cases of chronic infection but is rare in disseminated disease.
6. Multiple-stool smear for detection of larva is gold standard for diagnosis of strongyloidiasis.
7. Infection, even if asymptomatic, warrants treatment and proper follow-up by fecal smear examination after completion of therapy.
8. Ivermectin is the drug of choice.
9. Screening of patients (especially with peripheral eosinophilia) for strongyloid infection prior to immunosuppressive therapy can prevent fatalities due to disease.
10. Treating physicians need to be aware of the condition to prevent delay in diagnosis.

Chapter 32.12

Trichinosis

Akash Bang, Puja Hingorani

Trichinosis (or trichinellosis) is a parasitic infection caused by the nematode *Trichinella*, most commonly acquired through the consumption of the undercooked meat.

EPIDEMIOLOGY

Trichinosis is distributed all over the world, but most commonly in Asia, Latin America and Central Europe. Cases usually tend to cluster among groups that have consumed meat from a common infected source. Since undercooked meat is the common source of infection in humans, cultural factors and food preferences play an important role in the epidemiology. Cattle and other pure herbivores are not naturally infected, so people preferring beef are not at high-risk unless there is contamination with the pork. Sanitation is another important environmental determinant. Poor disposal of the animal meat, carcasses or dead bodies increase the risk of circulation of *Trichinella* in the peri-urban animals like pigs who become infected after feeding on such infectious source. Also, hunting and eating wild animals increases the risk. Human travel, translocations of animal populations and export of food have further contributed to the reemergence of the disease.

ETIOLOGY

Human trichinosis is caused by the tissue-dwelling nematode, *Trichinella*. *Trichinella spiralis* is the commonest species and is found worldwide in a variety of carnivorous and omnivorous animals. It shows encystment and infects only mammals. There are seven more species of *Trichinella*, some of which do not show encystment and also infect birds and reptiles in addition to mammals.

LIFE CYCLE

Trichinella exists in two types of life cycles: (i) a domestic cycle involving pigs, rodents, horses, etc., and (ii) a sylvatic cycle involving wild animals. Human infection occurs upon ingestion of inadequately cooked infected meat that contains the encysted larvae. Most frequent source is the undercooked pork. On exposure to the gastric acid and pepsin, the cyst walls are digested in the stomach and the larvae are released. They pass into the small intestine and invade the small intestine columnar epithelium at the villi base where they develop into adult worms around 1–2 mm in length. Fertilized female worms start releasing new larvae about 1 week after ingestion and continue for next 3–4 weeks. The life of an adult worm in intestine is around 4 weeks after which they are expelled in feces. The larvae released by the adult females invade the circulation and migrate to the striated muscles. In the striated muscles the larvae burrow into individual muscle fibers, increase up to 10 times in length and undergo encystment (Fig. 1). Encysted larvae can remain viable for years and can infect a new host if ingested.

PATHOGENESIS

In the initial couple of weeks after infection, the gastrointestinal tract gradually shows a mild, partial villus atrophy and an inflammatory infiltrate in the mucosal and submucosal layers.

The larvae released by adult female worms disseminate over the next several weeks. Skeletal muscle fibers may show edema,

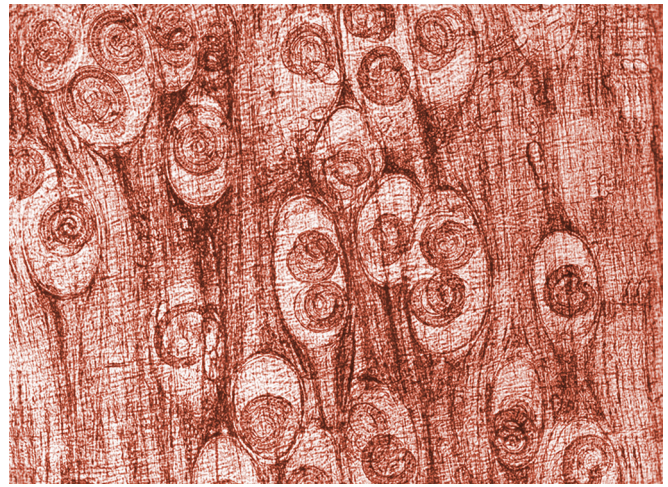


Figure 1 *Trichinella spiralis* cysts seen embedded in a muscle tissue specimen
Source: Public Health Image Library (PHIL), CDC, USA.

basophilic degeneration and a coiled encysted worm surrounded by lymphocytic and eosinophilic infiltrate.

CLINICAL FEATURES

The severity of infection depends on the ingested larvae load. The incubation period is usually 1–4 weeks and also depends on ingested larvae load, host immune status and the invasiveness of the species of *Trichinella*. Mild infections can be subclinical without any marked symptoms or signs. Clinically apparent trichinosis usually follows two stages:

1. **Intestinal stage** This stage occurs between 2 days and 7 days after ingestion and correlates with the release of the encysted larvae from the ingested meat in the stomach due to acid-pepsin digestion, their burrowing into the intestinal mucosa and maturation into adult worms. Diarrhea is the commonest complaint. Other clinical features include abdominal pain, nausea and vomiting. Reinfection in patients with previous infection and sensitization may cause a persistent diarrhea lasting for weeks. Extremely high worm load may cause a fulminant enteritis.
2. **Muscle stage** This stage occurs after 1 week after ingestion and correlates with the hematogenous spread of the larvae, their entry into skeletal muscles and the subsequent inflammatory reaction. Clinical features include extreme muscle pain which at times may limit all movements, high fever, muscle swelling, tenderness and weakness. Usually affected areas include calves, forearms, upper arm, neck and shoulder girdle. Subungual splinter hemorrhages (Fig. 2), conjunctival or retinal hemorrhages, periorbital edema and chemosis, vision disturbances, headache and ocular pain may be observed. Less common manifestations are macular, petechial or urticarial rash, cough, dyspnea, dysphagia, and hepatomegaly. Severe infections may lead to death due to myocarditis, encephalitis or pneumonia. As the encystment occurs, clinical manifestations gradually resolve. Encysted larvae can persist for several years before they calcify and die.

Ocular Manifestations of Trichinosis

These need special mention as many times patients may present only because of various ocular manifestations which result from larval invasion into the extraocular and the orbicularis

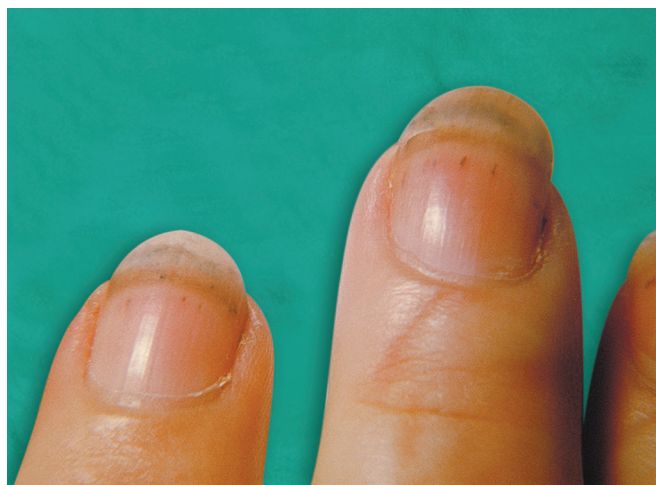


Figure 2 Trichinosis is manifested by splinter hemorrhages under the finger nails

Source: CDC/Thomas F Sellers/Emory University; Public Health Image Library (PHIL), CDC, USA.

muscles. Most characteristic and notable ocular manifestation is chemosis of the bulbar conjunctiva with slight inflammatory reaction (classically described as *pale lemon jelly appearance*) that is limited usually to the conjunctiva overlying the medial and lateral recti muscles and fading out to the limbus due to the early invasion of the recti muscles by *Trichinella*. Other frequently associated features include lid edema slowly progressing to surrounding areas causing the typical periorbital puffiness, painful eye movements, exophthalmos, pupillary dilation, conjunctivitis, subconjunctival hemorrhages and both superficial and deep retinal hemorrhages.

DIAGNOSIS

Diagnosis is based on clinical features and is confirmed by serology and/or muscle biopsy.

Clinical features of muscle pains, fever and periorbital edema with a history of ingestion of either inadequately cooked meat (especially pork) or a meat source also ingested by other symptomatic individuals should strongly indicate trichinosis.

Laboratory abnormalities appear during the muscle stage. Eosinophilia is the hallmark and in the 2nd–4th week after infection, eosinophils may constitute up to as much as 90% of the leukocyte count. Degree of eosinophilia is not a prognostic indicator. Sudden eosinopenia may develop secondary to inflammation or due to secondary bacterial infection and is considered a poor prognostic sign. Other possible abnormalities include leukocytosis, elevated creatine kinase and lactate dehydrogenase and hypergammaglobulinemia.

Serological tests include enzyme-linked immunosorbent assays (ELISA), indirect immunofluorescence, latex agglutination tests and are generally reliable but not very useful for early diagnosis since antibodies are detectable only after about 3 weeks after the infection. Also, antibody titers do not correlate with the clinical severity and may remain elevated for years after symptoms subside. Autoimmune diseases and other helminthiasis can give a false-positive antibody test.

Muscle biopsy is confirmatory but rarely needed. The biopsy should be taken from the swollen, tender muscle, preferably near the tendinous insertion. The Centers for Disease Control

and Prevention (CDC) diagnostic criteria for trichinosis requires positive serology or muscle biopsy for *Trichinella* with one or more compatible clinical symptoms such as eosinophilia, fever, myalgia and periorbital edema and history of consumption of potentially contaminated meat.

MANAGEMENT

Mild, subclinical or asymptomatic infections are self-limiting and do not need any anthelmintic treatment. Children below 2 years of age also should not be given anthelmintic therapy. Such patients can be managed symptomatically. Symptomatic management includes management of diarrhea, prevention and treatment of dehydration, antiemetics, analgesics and anti-inflammatory agents for fever, muscle pains. Ocular steroid drops and ointments may relieve the chemosis and ocular pain. Severe ocular pain may require retrobulbar injection of triamcinolone.

For intestinal stage, albendazole (400 mg orally twice a day for 8–14 days for all ages above 2 years) or mebendazole (200–400 mg orally thrice a day for 3 days, then 400–500 mg thrice a day for 10 days for all ages above 2 years) should be administered. For muscle stage, there is no consensus for treatment. Systemic corticosteroids (prednisolone 2 mg/kg/day for 10–14 days) may be added to the above anthelmintic therapy in severe infections especially if there are neurological, cardiac, pulmonary, or such systemic symptoms (**Box 1**).

PREVENTION

Health education and public awareness about avoiding consumption of raw or inadequately cooked meat forms the mainstay of the primary prevention. Public health measures that can reduce infection with *Trichinella* include stringent rodent control, prevention of exposure of pigs and other livestock to animal carcasses or to wild animals and certification of meat products.

BOX 1 Summary of trichinosis

Clinical features:

- Intestinal stage (1st week): Diarrhea, abdominal pain, vomiting
- Muscle stage (2nd–4th week and beyond): Fever, myalgia, muscular tenderness and swelling, periorbital edema
- Complications: Encephalitis, pneumonia, myocarditis.

Investigations:

- Complete blood count: Eosinophilia, leukocytosis
- Elevated muscle enzymes: Creatine kinase, lactate dehydrogenase
- Hypergammaglobulinemia
- Serological tests to detect antibodies: ELISA, latex agglutination, immunofluorescence
- Muscle biopsy.

Diagnostic criteria (CDC): (All three criteria required)

- History of ingestion of undercooked meat
- Compatible clinical features (muscle pains, fever, eosinophilia) and
- Positive serology or muscle biopsy.

Treatment:

- Mild/asymptomatic/subclinical infections or age below 2 years: Symptomatic
- Severe infection and age above 2 years: Albendazole 400 mg PO BID for 8–14 days or mebendazole 200–400 mg PO TID for 3 days, then 400–500 mg PO TID for 10 days
- Systemic complications: Add prednisolone 2 mg/kg/day for 10–14 days

IN A NUTSHELL

1. Trichinosis is caused by the nematodes of *Trichinella* genus. Pigs are the most common source of infection and mode of transmission is ingestion of undercooked meat.
2. Severity of infection depends on the ingested larvae load. Mild infections are asymptomatic. Heavy infections present with the intestinal stage in the 1st week of infection and muscle stage in next 3–4 weeks. Complications include encephalitis, pneumonia or myocarditis.
3. Diagnosis requires history of consumption of potentially contaminated meat, one or more compatible features such as eosinophilia, fever, myalgia and periorbital edema and either a positive serology or muscle biopsy. Serology is not useful in the first 2–3 weeks of infection. Eosinophilia develops during the 2nd week of the muscle stage.
4. Most infections are uncomplicated, self-limited, mild and do not require anthelmintics. Severe trichinosis with systemic symptoms should be treated with albendazole or mebendazole.

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Chapter 32.13

Filariasis

Ajay Gaur

Filarial worms are arthropod transmitted nematodes or round-worms that dwell in the subcutaneous tissues and the lymphatics. Each goes through a complex life cycle that includes an infective larval stage carried by the insects and an adult worm stage that resides in humans either in the lymph nodes or adjacent lymphatics or in the subcutaneous tissue.

The adult female worm produces *microfilariae*. These offspring either circulate in the blood or migrate through the skin. The microfilariae can be ingested by the appropriate biting arthropod and develop into infective larvae that are capable of initiating the life cycle once more (*Wuchereria bancrofti*), circulate in the blood with defined circadian rhythm or *periodicity* which can be nocturnal (typically the lymphatic filariae). When absent from the peripheral blood, the microfilariae of filarial parasites are found in the deeper visceral capillaries, particularly in the pulmonary capillaries. Adult worms are long-lived, whereas the life spans of microfilariae range from 3 months to 3 years.

EPIDEMIOLOGY

Lymphatic filariasis (LF) is caused by three species, *W. bancrofti*, *Brugia malayi* and *Brugia timori* which together infect an estimated 120 million persons in Africa, southern Asia, the western Pacific Islands, the Atlantic coast of south and central America and the Caribbeans particularly Haiti and the Dominican Republic. Countries with the highest prevalence include India, Indonesia, Papua New Guinea, Nigeria, Ghana, Kenya and Tanzania. Most heavily infested areas in India are the states of Andhra Pradesh, Tamil Nadu, Kerala, Orissa, Bihar and eastern Uttar Pradesh. In India, most of the cases (98%) are accounted for by bancroftian filariasis which is mostly found in Kerala. There is no animal reservoir for *W. bancrofti*.

The various human parasites in this category (Table 1) have certain characteristics in common. They all are spread by vectors and the adults invade and occupy the lymphatics, skin, connective tissue or blood. They produce live embryos called microfilariae that enter bloodstream or skin where they can survive for months or years with further development. The range of disease caused by

these worms is wide; some produce no symptoms whereas others can be responsible for severe clinical disorders.

PATHOPHYSIOLOGY

The primary pathology is compromised lymphatic function. Adult worms induce lymphatic dilatation that results in lymphatic dysfunction, lymphedema and a greater susceptibility to bacterial infection. The consequent inflammation, plus that caused by host responses to dying parasites, damages the delicate lymphatic vessels and compromises lymphatic function further. When such processes occur in lymphatic vessels of the scrotum, hydrocele develops. Live motile worms exhibiting the *filarial dance* sign and nearby dilated lymphatic vessels can be detected by ultrasonography of the scrotum, inguinal lymph node and breast. Microfilaremia often is *asymptomatic*, but frequently associated with immune complex nephritis; more rarely, the microfilariae can be target of immunologic hyper responsiveness and result in a severe *tropical pulmonary eosinophilia* (TPE) syndrome.

It is not clear why the majority of infected individuals remain asymptomatic while others develop acute or chronic manifestations of lymphatic filariasis. Many persons with chronic lymphedema of the extremities have no evidence of active infection (particularly in India), whereas this is not the case in other *W. bancrofti* endemic areas such as Papua New Guinea. Adaptive T-cell responses, genetic susceptibility, worm burden and innate immunity to the *Rickettsia* like endosymbiont *Wolbachia* of filarial parasites have been suggested to contribute to the complex clinical phenotypes of lymphedema and hydrocele, but a single unifying mechanism is not defined.

LIFE CYCLE

Infection is initiated when female mosquitoes release infective 3rd stage larvae into the puncture site of the skin created during blood feeding. These larvae pass rapidly through the dermis and enter local lymphatic vessels where they molt to form 4th stage larvae. Over 6–9 months, the parasites undergo another molt in afferent lymphatic vessels and eventually develop into sexually mature adult male and female worms. Adult worms largely reside in afferent lymphatic vessels of the upper and lower extremities and the lymphatic of the male genitalia, such as those draining the epididymis, testicles and spermatic cord. Other areas of the body may also harbor adult worms such as skin. Fecund female worms release as many as 10,000 1st stage larvae (commonly referred to as microfilariae) per day, which migrate from the lymphatics

Table 1 Characteristics of filarial parasites

Species	Adult	Microfilaria	Geographic distribution	Vector	Periodicity	Location	Size (μm)	Tail	Sheath	
									Presence	Staining properties
<i>Wuchereria bancrofti</i>	Lymphatics	Blood	Tropics worldwide	Mosquitoes	Nocturnal or sub-periodic	Blood, hydrocele fluid	298 by 7.5–10	Pointed tail devoid of nuclei	+	Does not stain
<i>Brugia malayi</i>	Lymphatics	Blood	Southeast Asia	Mosquitoes	Nocturnal or sub-periodic	Blood	270 by 5–6	Nuclei in tail	+	Bright pink with Giemsa
<i>Brugia timori</i>	Lymphatics	Blood	Indonesia	Mosquitoes	Nocturnal	Blood	300 by 5–6	Nuclei in tail	+	Tends not to stain
<i>Loa loa</i>	Connective tissue	Blood	West and Central Africa	Deer fly (chrysops)	Diurnal	Blood	Up to 300	Irregularly arrange red nuclei extend to end of tail	+	Does not stain

and enter the bloodstream. Microfilariae in peripheral blood are ingested by mosquitoes and undergo development to infective 3rd stage larvae after completing two molts in the mosquito over a period of 14 days. Adult worms are larger than microfilariae ($100 \times 0.25 \text{ mm}$ and $150 \times 7 \mu\text{m}$ respectively) and have reproductive life span of 5–7 years. A characteristic feature of LF in most endemic areas is the nocturnal periodicity of microfilaremia. Peak levels of parasites appear in peripheral blood at night when the mosquito vectors are seeking a blood meal. During the day, microfilariae are sequestered in deep vascular beds and may not be detectable in peripheral blood (**Fig. 1**).

CLINICAL FEATURES

Lymphatic filariasis is associated with a variety of clinical manifestations. The four most common presentations are asymptomatic (or subclinical) microfilariaemia, lymphedema, hydrocele and acute attacks. Less frequently LF can present with chyluria or tropical eosinophilia. The range of clinical disease varies across geographic locations and according to the species of nematode causing the infection. The early signs and symptoms include episodic fever, lymphangitis of an extremity, lymphadenitis (especially the inguinal and axillary areas), headache and myalgia that last a few days to several weeks. These symptoms are caused by an acute inflammatory response triggered by death of adult worms.

Most infected persons are asymptomatic, filarial lymphadenopathy is seen commonly in infected children, before puberty.

Adult worms can be detected by ultrasonography of the inguinal and axillary lymph nodes and vessels. In boys after puberty, the adult worms tend to live in the intrascrotal lymphatic vessels. Ultrasonography of lymphatic vessels may reveal motile adult worms termed the *filarial dance sign*. Even in asymptomatic people, the presence of living adult worms leads to lymphatic dilatation and abnormal lymph flow which can be demonstrated by lymphoscintigraphy. These changes predispose the person to lymphedema. Lymphatic vessel dilatation and lymph node enlargement and fibrosis also can be visualized when lymph nodes are examined histopathologically. Microscopic hematuria and proteinuria also are found.

A separate and clinically distinct syndrome, which for years was confused with filarial lymphangitis, is acute dermatolymphangioadenitis caused by bacterial infection of the small collecting lymphatic vessels in areas of lymphatic dysfunction. Unlike true filarial lymphangitis, this syndrome develops in a reticular rather than a linear pattern and is more commonly associated with severe pain fever and chills.

Lymphedema occurs in the legs, scrotum, penis and arms. In the legs and arms, it is usually unilateral. The most important factor involved in progression of filarial lymphedema to elephantiasis is repeated episodes of acute dermatolymphangioadenitis, originating from breaks in the epidermis, which contribute to further lymph stasis, secondary bacterial infection and fibrosis.

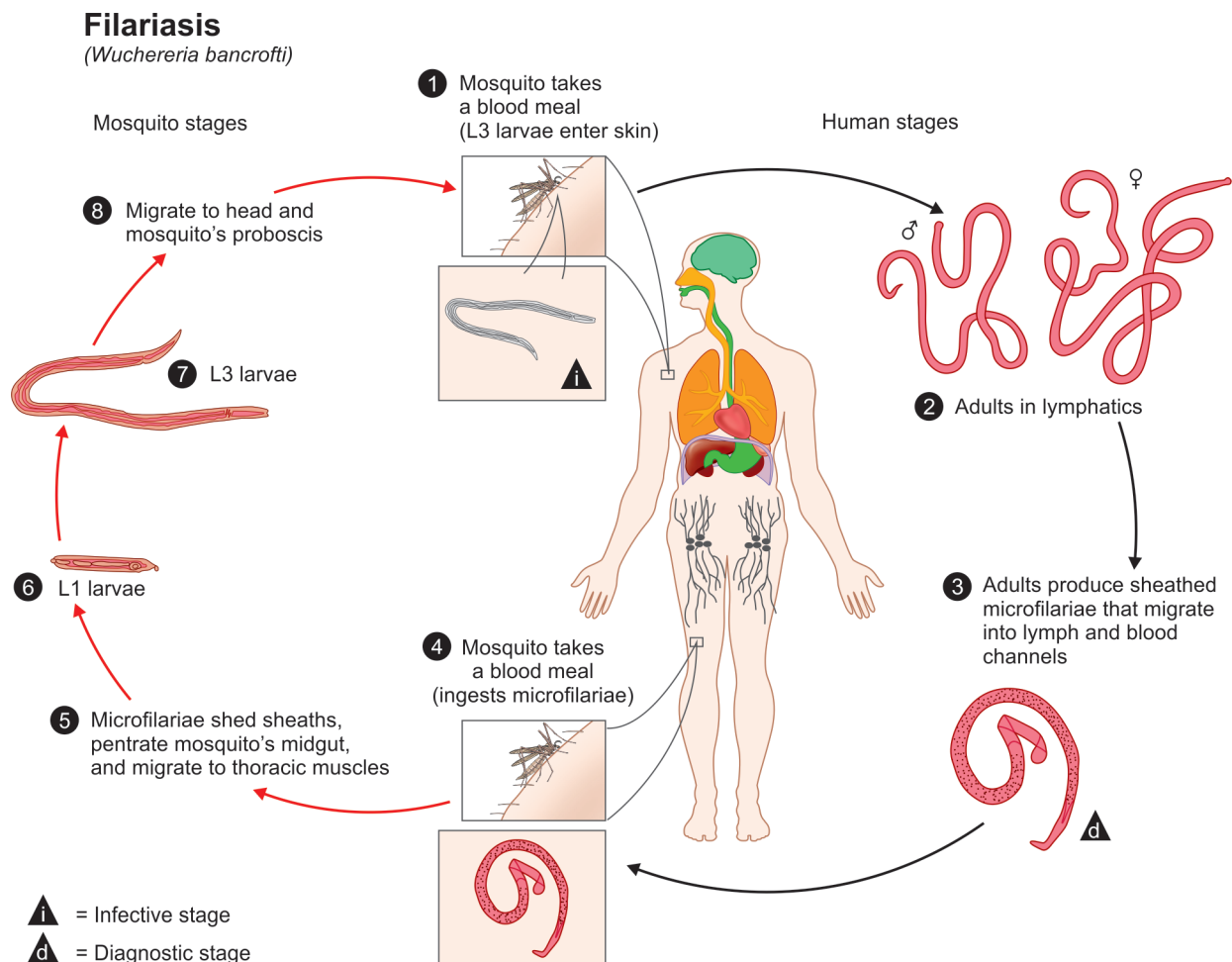


Figure 1 Life cycle of *Wuchereria bancrofti*

Source: CDC/Alexander J da Silva/Melanie Moser. Public Health Image Library (PHIL), CDC, USA.

Tropical Pulmonary Eosinophilia

Tropical pulmonary eosinophilia is a distinct syndrome that develops in some individuals infected with LF species. This syndrome affects males more often than females, most commonly during the third decade of life. The main features include a history of residence in regions where filariae are endemic, paroxysmal cough and wheezing that are usually nocturnal, weight loss, low-grade fever and adenopathy. Patients are rarely found to have microfilariae in the blood. The X-ray findings may occasionally be normal, but increased bronchovascular markings discrete opacities in the middle and basal regions of the lung or diffuse miliary lesions are usually present. Recurrent episodes may result in interstitial fibrosis and chronic respiratory insufficiency in untreated individuals. Tests of pulmonary function show restrictive abnormalities in most cases and obstructive defects in one-half of the cases. Total serum immunoglobulin E (IgE) levels (10,000–100,000 ng/mL), peripheral blood eosinophilia ($>2,000$ cells/mm³) and antifilarial antibody titers are characteristically elevated. TPE is considered to be a form of occult filariasis, in which rapid clearance of the microfilariae occur, presumably on the basis of host immunologic hyper responsiveness to the parasite. Although there is no single clinical or laboratory criterion that aids in distinguishing TPE from other pulmonary disease; residence in the tropics, the presence of high levels of antifilarial antibodies and a rapid clinical response to diethylcarbamazine (DEC) favor the diagnosis of TPE. The clinical response to DEC (2 mg/kg/dose TID PO for 12–21 days) is the final criterion for diagnosis; the majority of patients improve with this therapy.

DIAGNOSIS

Direct Examination

A definitive diagnosis is made by microscopic detection of microfilaria in the blood or occasionally from other sites such as fluid aspirated from hydrocele. The circulation of microfilariae in peripheral blood is periodic with highest concentrations occurring at night, therefore blood specimens should be collected between 10 pm and 2 am. Microfilariae of the three species are distinguished morphologically. Because infected children are frequently microfilaria negative, other tests may be helpful in making the diagnosis. Long et al. describe an interesting approach to the laboratory diagnosis of filariasis using an acridine orange serves as the basis for this test. On centrifugation, parasites become concentrated in the buffy coat and can be visualized through the clear glass wall of the tube. The acridine orange stains the DNA of the parasites and the morphologic characteristics including the nuclear patterns in the tail sections can be examined by fluorescence microscopy in making a species identification. Because microfilariae may be present in the blood in only small numbers, sensitive procedures such as nuclepore filtration and Knott's concentration are also used routinely to detect infections.

Antigen Detection

Assays for circulating antigens of *W. bancrofti* permit the diagnosis of microfilaremic and cryptic infection. Two tests are commercially available. One is an enzyme-linked immunosorbent assay (ELISA) and other is a rapid format immunochromatographic cartridge. Both assays have sensitivities that range from 96% to 100% and specificities that approach 100%. Both tests can be used on blood drawn any time of day or night, thus avoiding the need for specific bleeding times depending on periodicity of microfilariae.

Nucleic Acid Detection Techniques

The advent of polymerase chain reaction (PCR) assays is proving to be useful not only in establishing a diagnosis, but also for use

in monitoring therapy and in discrimination between past and present infection. PCR based assays that detect as little as one microfilaria per milliliter of blood have been described. PCR can detect parasite DNA and is now the most sensitive technique for definitive diagnosis. For each of the lymphatic dwelling parasites, primers and probes have been identified that are 100% specific and provide sensitivities that are up to ten folds greater than parasite detection by direct examination.

Serologic Tests

Immunologically based diagnosis with measured IgG or IgG4 responses against crude extracts of *Brugia* worms suffers from poor specificity. There is extensive cross-reactivity among filarial antigens and antigens of other helminths including the common intestinal roundworms. Further serologic tests are unable to distinguish between active and past infection. These tests still have a role in diagnosis as a negative test effectively excludes past or present infection.

TREATMENT

The use of antifilarial drugs in the management of acute lymphadenitis and lymphangitis is controversial. DEC can be given to asymptomatic children to lower down parasitemia. It also kills adult worms. Whether DEC modifies the course of disease is not proven. New agents or drug regimens are needed that would be more effective against the adult filarial worm and at the same time elicit minimal immunopathologic damage.

Currently, the major drugs used are especially effective against microfilariae. DEC is the treatment of choice and given in a 1 mg/kg as a single dose on day 1, increased to 1 mg/kg three times on day 2, on day 3 it will be 1–2 mg/kg three times and 6 mg/kg/day (in three divided doses) from days 4–14. More recently, a single dose of 6 mg/kg divided in three doses has been recognized to produce a similar therapeutic result in children with no microfilaria in the blood. Repeat doses may be necessary to further reduce microfilaremia and kill adult parasites. *W. bancrofti* is more sensitive to this drug than *B. malayi*. DEC may cause pruritus, fever, generalized body pains and hypotension; these side effects may be avoided by administering DEC in a graded, stepwise manner. This drug is also the treatment of choice for tropical pulmonary eosinophilia, a syndrome caused by circulating microfilariae.

Ivermectin may also have a role in the medical treatment of LF because it is very effective in clearing circulating microfilariae. Albendazole in high doses inhibits microfilarial production. The difficulty in management of filariasis by drugs is that late symptoms, such as elephantiasis, do not abate. The main utility of chemotherapy is in cases recognized early, before the anatomic abnormalities develop. Hydrocele can be treated surgically. Of critical importance in the management of lymphedema and elephantiasis is attention to hygiene, wearing shoes to prevent injury and reduction of lymphostasis with exercise and elevation of the lower extremity.

The more recent discovery that *W. bancrofti* harbors bacterial endosymbionts has led to use tetracycline and related antimicrobial agents as a part of the therapeutic regimen. This is under active investigation.

PREVENTION

Prevention in the past depended principally on vector. This is a difficult task since effective insecticides that also would be nontoxic to the rest of the environment are not available. Global Alliance to Eliminate Lymphatic Filariasis (GAELF) is directing a large scale LF control campaign through single dose combination of albendazole (400 mg) with either ivermectin (200 µg/kg) or DEC (6 mg/kg) in areas endemic for lymphatic filariasis.

IN A NUTSHELL

1. Filarial worms are arthropod transmitted nematodes or roundworms that dwell in the subcutaneous tissues and the lymphatics.
2. All filariae share is the unique characteristic, with defined circadian rhythm or *periodicity*, which can be nocturnal.
3. Most heavily infested areas in India are the states of Andhra Pradesh, Tamil Nadu, Kerala, Orissa, Bihar and eastern Uttar Pradesh.
4. The pathology of LF is caused principally by the adult-stage parasite; induce lymphatic dilatation that results in lymphatic dysfunction.
5. Microfilariae in peripheral blood are ingested by mosquitoes and undergo development to infective 3rd stage larvae over a period of 14 days.
6. The four most common presentations are asymptomatic (or subclinical) microfilaremia, lymphedema, hydrocele and acute attacks.
7. A definitive diagnosis of LF can be made by microscopic detection of microfilaria in the blood or occasionally from other sites such as fluid aspirated from hydroceles.
8. DEC is the treatment of choice and can be used in asymptomatic children to lower down parasitemia load.

MORE ON THIS TOPIC

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Chapter 32.14

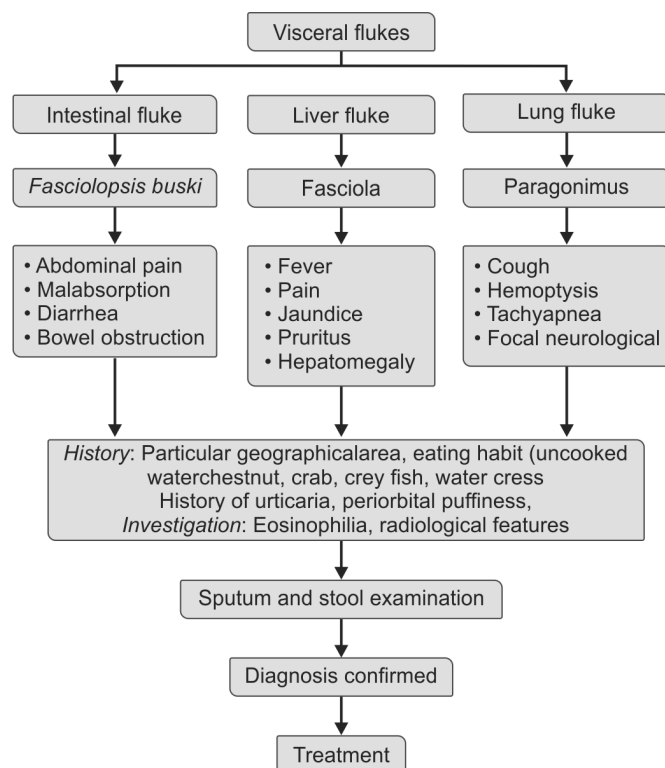
Intestinal, Liver and Lung Flukes

Vikas Jain

Trematode infections (blood flukes and visceral flukes of intestine, liver, lung) are uncommon helminthic infections. Species belonging to eight genera commonly infect human visceral organs (intestine, liver and lung). Visceral flukes are food-born zoonotic infections with complicated life cycle which are emerging as public health problem worldwide. Although most of available adult studies related to visceral flukes are reported from different Southeast Asia countries, but literature from India especially in children is usually unrecognized. It is due to ignorance and lack of medical health facilities in rural and coastal areas where these infections are common. Common visceral flukes in Southeast Asia region are **intestinal flukes** (*Fasciolopsis buski*, *Heterophyes heterophyes*, *Metagonimus yokogawai*, *Echinostoma ilocanum*), **liver flukes** (*Fasciola hepatica*, *Fasciola gigantica*, *Clonorchis sinensis*, *Opisthorchis viverrini*) and **lung flukes** (*Paragonimus westermani*) (Flow chart 1).

Visceral flukes are most commonly prevalent in rural or coastal areas where poor sociocultural food habits are conducive for transmission of these infections. Visceral flukes are commonly seen in Southeast Asia but exact data on geographical distribution of different flukes are not available. Flukes are most commonly reported from Northeast states of India. Most of Indian data are in form of case reports and case series in adults.

Flow chart 1 Approach to visceral fluke



INTESTINAL FLUKES

Fasciolopsis buski is an intestinal fluke with maximum infections occurring during late summer and early autumn. Intestinal fluke infections are commonly associated with poor socioeconomic factors such as poverty, malnutrition, lack of sanitation and tradition of eating raw or insufficiently cooked food.

Etiology

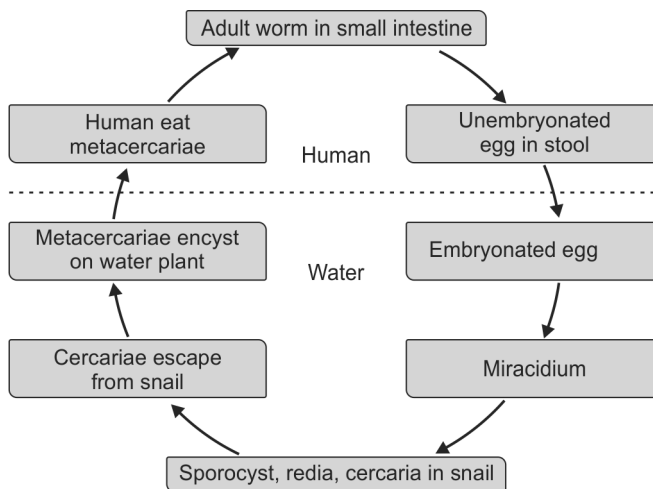
It was first described in 1843 in duodenum of Indian man by Busk. The major mode of human infection is consumption of raw or improperly cooked aquatic plants such as water chestnut, water hyacinth, water bamboo and other aquatic vegetation. Pigs are the main source of eggs and drainage of pig excreta in farms is an important factor for maintaining high endemicity. Prevalence of infection with *F. buski* in Southeast Asia countries varies from 10% in Thailand to 57% in China; data from India is sketchy.

Life Cycle

Fasciolopsis buski (giant intestinal fluke) is the largest fluke, 20–75 mm in length and 8–20 mm in width, lives in duodenum and jejunum of pigs and human where fluke lays eggs. These eggs are passed in stool and become embryonated in water in 6–7 weeks. Mature miracidia hatch from egg in water and then invade a suitable snail intermediate host, in which further developmental stages (sporocysts, rediae, cercariae) occur. Finally, cercariae escape from snail into water to encyst as metacercariae on aquatic plants. Mammalian hosts (humans and pigs) are infected if they eat these plants (Fig. 1). In the human host, metacercariae excyst and attach to duodenum and jejunum where they become adult flukes within 3 months. Life span of adult fluke ranges from 6 month to 1 year.

Pathogenesis

Adult *F. buski* produces traumatic, toxic and obstructive damage to the intestinal mucosa. It causes local mucosal inflammation along with hypersecretion of mucus, hemorrhage and ulceration. Large numbers of flukes can obstruct and even perforate the lumen. It may produce the disease by allergic mechanism due to absorption of worm metabolites in heavy infections.

Figure 1 Life cycle of *Fasciolopsis buski*

Clinical Features

Manifestations depend upon the parasitic load. Nausea, abdominal pain and diarrhea are nonspecific symptom. Heavy infections result in profuse yellow-green diarrhea with features of malabsorption due to protein losing enteropathy, vitamin B₁₂ deficiency and anemia. Large parasite load may cause bowel obstruction, acute ileus and allergic reaction due to absorption of toxic metabolites of worms. Periorbital puffiness and ascites may occur. Intestinal perforation due to *F. buski* is reported from India in a child.

Diagnosis

Complete blood count may show anemia, eosinophilia and leukocytosis. Serum albumin is low due to protein losing enteropathy. Wet stool preparation (by formalin-ethyl acetate sedimentation concentration method) shows unembryonated, ellipsoidal, 130–140 µm by 80–85 µm, operculated egg. The eggs of *F. buski* and *F. hepatica* are similar in size and shape. Exact identification of species can be done by internal transcribed spacer (ITS) sequences of ribosomal DNA. Upper gastrointestinal endoscopy may show adult fluke moving in duodenum (**Figs 2A and B**).

Management

Tetrachlorethylene, the initial drug of choice, is now replaced by praziquantel as the preferred treatment. Praziquantel is administered as a single oral dose of 15 mg/kg after evening meal or before sleep. Adverse effects include abdominal pain, headache, nausea and dizziness. Contraindication includes ocular cysticercosis and pregnancy.

Prevention

Avoid eating raw aquatic plant foods like water chestnut. Either it should be peeled off or immersed in boiling water for few minutes before consumption. Other preventive measures include sterilization of night soil before being used as fertilizer and avoiding defecation near ponds or lakes.

LUNG FLUKES

Paragonimus westermani is most common species for paragonimiasis in humans. Of late, *Paragonimus heterotremus* has also been increasingly detected in humans especially in Southeast Asia. Human paragonimiasis is caused by eating undercooked crabs, crayfish and undercooked pork. First time, it was reported in humans from Taiwan following which diagnosed worldwide

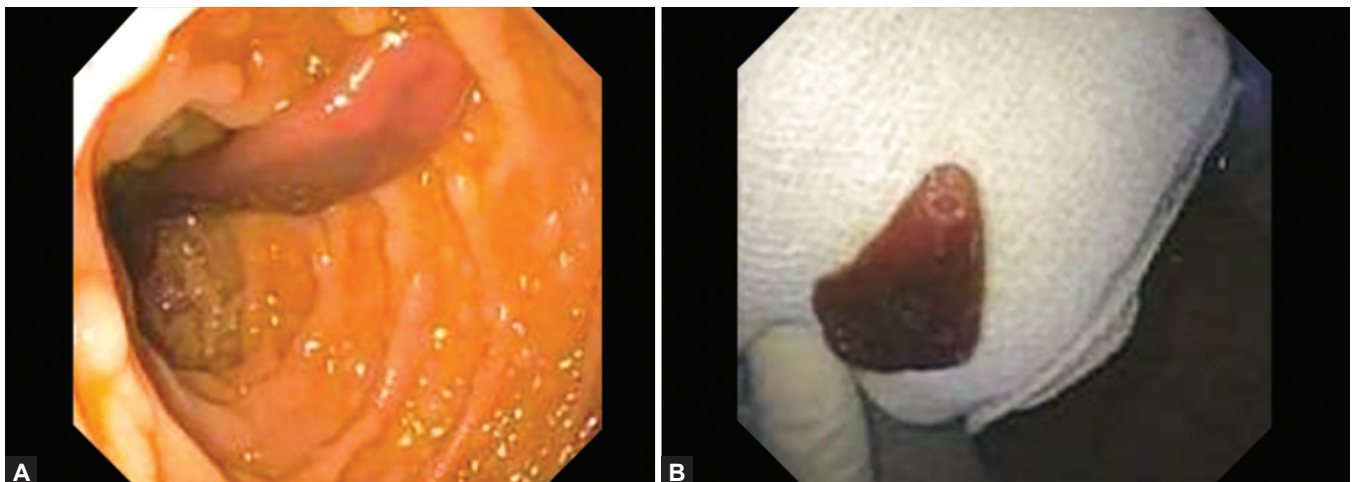
mainly in orient countries such as Japan, South Korea, Thailand, China and Philippines. In India, it is endemic in Northeast states, as in some parts of Arunachal Pradesh. First indigenous case of human paragonimiasis was reported from Manipur in 1981; subsequently 39 more patients of pulmonary paragonimiasis were described in 1986. One Indian study of 45 cases showed varied clinical presentation in children. This disease is still under reported in children due to ignorance of disease and lack of health facilities in difficult geographical area. Clinical implication of pulmonary paragonimiasis is important as it is commonly misdiagnosed as tuberculosis in Indian setting.

Pathogenesis

Paragonimus westermani is 7–12 mm in length and 4–6 mm in width, and normally resides in bronchioles in paired form where it lays eggs. Eggs are coughed out in sputum. Some eggs are swallowed in sputum which subsequently pass in stool. Eggs hatch in water and release miracidia after 2–3 weeks that invade a suitable snail intermediate host, in which further developmental stages (sporocysts, rediae, cercariae) occur. Finally, cercariae escape from snail to infect the second intermediate crustacean host (crab and crayfish) which is eaten by humans who become infected. Metacercariae excyst in duodenum and traverse through intestinal wall into abdominal cavity then migrate through diaphragm into pleural cavity and lung where they become adult worm in the vicinity of bronchiole. Life cycle of *P. westermani* is depicted in **Figure 3**. Life span of adult fluke ranges from 1 year to 20 years. During migration, it can lodge in ectopic sites like brain and skin causing cerebral paragonimiasis and migratory subcutaneous nodules respectively. Small hemorrhagic inflammatory lesions may rarely form granuloma along the migration route of immature worm which otherwise are rarely symptomatic. Clinical symptoms arise mainly due to lung and brain lesion where mature worm induces intense inflammatory reaction and cyst formation occurs. The cyst constitutes rusty fluid, eosinophils, necrotic tissue, Charcot-Leyden crystals along with adult worms and ova. Symptoms usually occur due to rupture of bronchiole releasing necrotic material and blood in sputum.

Clinical Features

Clinical manifestations depend upon parasitic load. Symptoms usually occur in pulmonary, extrapulmonary (pleural, abdominal cavity, brain and skin) and pleuropulmonary forms. Pleural effusion and migratory subcutaneous nodules are more common in children (40–50%) than adults (2%).



Figures 2A and B *Fasciolopsis buski* in second part of the duodenum on gastroduodenoscopy

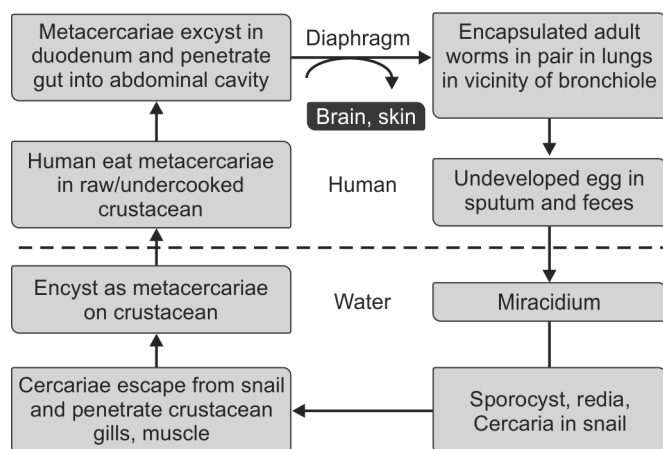


Figure 3 Life cycle of *Paragonimus westermani*

Pulmonary paragonimiasis is the commonest presentation of paragonimiasis. Most children are undiagnosed or asymptomatic. Symptomatic children present with recurrent hemoptysis, cough, respiratory distress, fever and other constitutional symptoms. The disease can be easily confused with pulmonary tuberculosis. Second common manifestation is pleural effusion that varies from minimal to massive effusion depending on worm load. Skin manifestations occur in the form of migratory subcutaneous nontender, mobile nodules. These occur in 10–15% of *P. westermani* infection in children; most common sites are chest, lower abdomen, thigh and inguinal region. Other presentation like pericarditis, organomegaly and nonspecific gastrointestinal symptom can occur. Cerebral paragonimiasis is the most serious extraintestinal form which is rarely reported in children. It usually presents with fever, headache, nausea, vomiting, visual disturbance and motor weakness. In India, first case of cerebral paragonimiasis mimicking tuberculoma in a child was reported from Nagaland.

Diagnosis

Complete blood count may reveal leukocytosis with relative lymphocytosis, eosinophilia, high ESR but anemia is rare in spite of repeated hemoptysis. Chest radiography can show consolidation, cavitory lesions, pleural thickening and pleural effusion. Microscopy and immunodiagnostic test are commonly used to detect infection.

Microscopy

Wet mount smear of sputum examination shows Charcot-Leyden crystals and paragonimus eggs which are ovoid brownish yellow, unembryonated, operculated, thick shelled with size 80–120 μm by 45–65 μm . Repeated examinations of sputum along with concomitant stool examinations increase the yield in mild infection.

Serology

Immunodiagnostic test like intradermal test, Dot-ELISA, complement fixation test are commonly used. Intradermal test is done by intradermal injection of 0.01–0.1 mL of purified antigen of adult *P. westermani* on front of the forearm. Wheal diameters greater than or equal to 5 mm with erythema and pseudopodia immediately and 15 min after the inoculation indicate positive test. Negative test almost certainly rules out paragonimiasis but positive test cannot differentiate between recent and past infection, also there is cross-reaction with other trematodes. ELISA using excretory-secretory antigen (27 kDa of *P. westermani*, 31.5 kDa of *P. heterotremus*) is highly sensitive and specific for detection

of active infection. Dot-ELISA has also been used for antigen detection in sera.

Management

Pulmonary paragonimiasis is rarely life-threatening, but cerebral paragonimiasis can be fatal. The drug of choice is praziquantel (25 mg/kg three times a day for 3 days after meal). Dose in cerebral paragonimiasis is generally higher. Preventive measures include avoiding eating raw uncooked crab and crayfish, proper sanitation and public health education.

LIVER FLUKES

Liver flukes (*F. hepatica*, *Clonorchis sinensis*, *O. viverrini*) are food-borne trematode infections. In Asia, *O. viverrini* (Thai liver fluke) is commonly prevalent in Thailand, Laos, southern Vietnam, Cambodia; and *C. sinensis* (Chinese liver fluke) is common in Korea, Taiwan, China, northern Vietnam. *F. hepatica* (sheep liver fluke) is found mainly in sheep and cattle raising areas, and around 2.4 million people worldwide are infected. In India, human fascioliasis has been reported from northeastern India including Bihar, Assam, Uttar Pradesh and Mumbai.

Fasciola Hepatica

Life Cycle

Fasciola hepatica measures 30 \times 13 mm and lives in bile ducts where it lays eggs. Eggs are carried by bile into intestine and subsequently in stool. Egg after 1–2 weeks hatches in water and releases miracidia that invade a suitable snail intermediate host in which further developmental stages (sporocysts, rediae, cercariae) occur. Finally, cercariae shed their tails and encyst on water vegetation (watercress) as metacercariae. Humans become infected after eating contaminated water vegetation. Encysted metacercariae excyst in human duodenum and traverse through intestinal wall into abdominal cavity, then migrate through liver parenchyma by penetrating capsule (acute hepatic phase) and finally enter the bile ducts where they become adult worm (chronic biliary phase). Adult worm produces egg which passes in the feces through bile (Fig. 4).

Clinical Features

Manifestations depend upon parasitic load and phase of infection. Manifestations range from completely asymptomatic infection in which fluke is detected incidentally during radiological and endoscopic evaluation for unrelated disease to florid manifestations. Allergic symptoms like fever, urticaria and abdominal pain may occur during acute migratory hepatic phase during migration of larva through liver parenchyma from intestine.

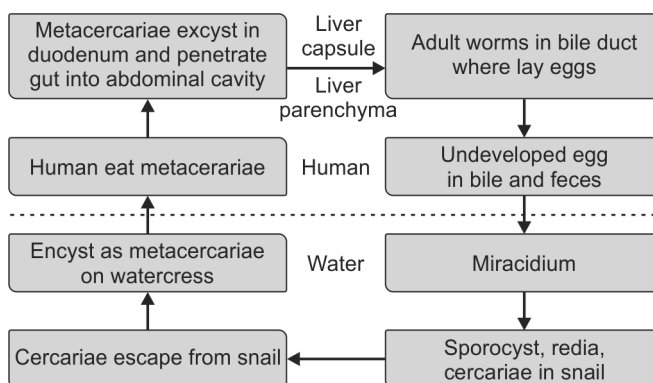


Figure 4 Life cycle of *Fasciola hepatica*

This phase is usually asymptomatic and starts 6–12 weeks after eating metacercaria and lasts for weeks to months. Larvae may be found in other organs like skin, brain and lungs. In second phase when worm establishes and matures in bile duct, it causes hyperplasia of biliary epithelium and fibrosis of bile duct that lead to biliary obstruction which manifests either as recurrent biliary colic or cholangitis (fever, jaundice, pruritus and hepatomegaly). Sometimes, the adult worm may reinvade the liver parenchyma causing liver abscess. Rarely, prolonged infection can cause cirrhosis and cholangiocarcinoma in adults. It is commonly misdiagnosed as choledocholithiasis.

Diagnosis

Complete blood count may show anemia, eosinophilia and leukocytosis. Liver function test may show raised alkaline phosphatase and conjugated hyperbilirubinemia.

Microscopy Wet mount stool examination after at least 3 days of liver free diet shows unembryonated, ovoid, 130–150 µm by 63–90 µm, operculated eggs. Eggs may also be retrieved from duodenal and biliary aspirates and tissue biopsy.

Serological methods These methods are useful in both the acute and chronic phase. Fas2-ELISA detects IgG antibodies against the antigen Fas2 and fasciola excretory-secretory (ES) in serum, feces and other fluids, also no cross-reactions observed with other parasitic infection. Other closely related species such as *F. gigantica* cannot be differentiated clinically from *F. hepatica*. Animal studies have reported a higher prevalence of *F. gigantica* infection than *F. hepatica*.

Polymerase chain reaction (PCR)-restriction fragment length polymorphism (RFLP) A simple PCR-RFLP assay, using the restriction enzymes *Ava*II and *Dra*II based on a 618-bp-long sequence of the 28S rRNA gene is described for the diagnosis of fascioliasis and also can differentiate between *F. hepatica* and *F. gigantica* infection.

Others Ultrasonography may show focal lesion in liver, dilated biliary radicles, biliary wall thickening and sometime echogenic worm. Endoscopic ultrasonography is good modality to screen lower common bile duct. If suspicion is high, endoscopic retrograde cholangiopancreatography (ERCP) may be useful for diagnostic and therapeutic intervention. Abdominal CT in the acute migratory phase reveals multiple small hypodense lesions and chronic phase may reveal hyperintense lesions 10–20 mm in diameter, which represents calcified dead flukes in the bile ducts, liver capsule thickening.

Management and Prevention

Triclabendazole is the drug of choice, administered as a single oral dose of 10 mg/kg, it acts by inhibiting protein synthesis, it has few side effects. Oral bithionol (30–50 mg/kg on alternate day for 10–15 doses) is also recommended but both drugs are not easily available. Praziquantel (25 mg/kg/day for 2 days after meal) is an alternative but resistance has been reported. Child may require endoscopic intervention in the form of endoscopic retrograde cholangiopancreatography with sphincterotomy for drainage of bile to relieve cholangitis. Rarely surgical intervention may be needed.

IN A NUTSHELL

1. Most common species of visceral flukes include *Fasciolopsis buski* (intestinal fluke), *Paragonimus westermani* (lung fluke), and *Fasciola hepatica* (liver fluke).
2. Humans are accidental intermediate hosts. Infection is acquired by eating uncooked aquatic water plant (*Fasciolopsis* or *Fasciola*), or crustaceans (*Paragonimus*).
3. Clinical features pertain to the primary organ where the fluke resides.
4. Diagnosis is established by documentation of eggs in wet stool; and endoscopy (*Fasciolopsis*), sputum examination (*Paragonimus*), or duodenal aspirate (*Fasciola*).
5. Drug of choice is Praziquantel for intestinal and lung flukes; and triclabendazole for the liver fluke.

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Chapter 32.15

Tapeworm Diseases

Ruchi Rai

Cestodes or tapeworms are segmented tape like worms which cause clinical disease in man. Humans are definitive hosts for all tapeworms with the exception of *Echinococcus* species, sparganosis and coenurosis. The infection with cestodes is common in India and other developing countries as the spread is facilitated by poor standards of hygiene. The infection gets transmitted by feco-oral route or ingestion of poorly cooked meat or fish. Medically important tapeworms are listed in **Box 1**.

BOX 1 Tapeworms causing disease in humans

- *Diphyllobothrium latum* (fish tapeworm)
- *Taenia solium* (beef tapeworm)
- *Taenia saginata* (pork tapeworm)
- *Echinococcus granulosus* (dog tapeworm)
- *Echinococcus multilocularis*
- *Hymenolepis nana* (dwarf tapeworm)
- *Hymenolepis diminuta* (rat tapeworm)
- *Dipylidium caninum*
- *Sparganum mansoni*; *S. proliferum*
- *Multiceps*

TAENIA SOLIUM (PORK TAPEWORM)

The infection is seen worldwide but incidence is high in countries of Africa, Latin America, East Europe and South East Asia especially, India. In 2003, World Health Assembly declared that *T. solium* is of worldwide public health importance. Intestinal infection is usually not seen in vegetarian population and those not consuming pork. The tissue cysticercosis can be acquired by vegetarians through contaminated water or vegetables. *Taenia asiatica* is a sister species of *Taenia saginata* found in Asia which causes similar illness in humans with pigs acting as intermediate host.

Etiology

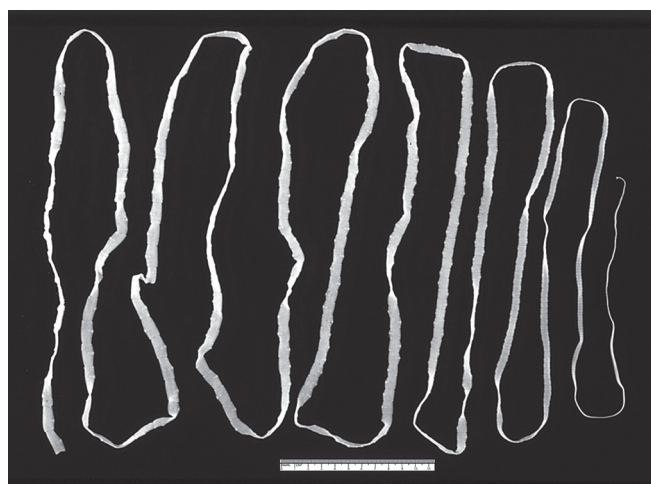
T. solium is also known as pork tapeworm as pigs are the intermediate host. Both the adult and the larval stages cause clinical disease in humans. The pigs get infected by ingesting fecal matter of humans containing eggs or proglottids of *Taenia*. The ova are ingested by the pigs and hatch into an embryo or oncosphere. These oncospheres, with the help of their hooklets penetrate the intestinal wall of the pig and reach the systemic circulation. They finally get lodged in the striated muscles and with time, evolve into mature larva or cysticercus cellulosae. The cysticerci are visible as tiny white dots in the infected pork (measly pork). Humans get infected when they eat raw or inadequately cooked pork. The head or the scolex (**Fig. 1**) emerges from the cysticercus and attaches to the intestinal wall and gradually develops into an adult tapeworm. The adult worm may be several meters long (up to 25 m) (**Fig. 2**). The adult worm has segments or proglottids which shed eggs in the stool. The humans can also get infected by the larval form by ingestion of eggs through contaminated water or vegetables, which leads to tissue cysticercosis in the same way as in pigs. Life cycle of *Taenia* is depicted in **Figure 3**.

Pathogenesis

The adult worm may compete with the child for nutrition or there may be a possibility of mechanical obstruction of the gut. The proglottids also escape from the anus leading to local symptoms. The cysticercosis may affect any organ or tissue of the body. The body responds to the

**Figure 1** Scolex of *Taenia solium*

Source: Public Health Image Library (PHIL), CDC, USA.

**Figure 2** Adult tapeworm; *Taenia saginata*

(Source: Public Health Image Library (PHIL), CDC, USA)

cysticerci by a tissue inflammatory and granulomatous response. Over a period of months to years the host response may lead to either resolution or calcification of these cysticerci.

Clinical Features

In spite of the length of the worm, children remain mostly asymptomatic or may have mild and vague symptoms. Some children may complain of abdominal discomfort or diarrhea. There may be loss of appetite and weight. Intestinal obstruction and appendicitis have rarely been reported. There may be anal pruritis because of the proglottids crawling out of the anus. Cysticercosis leads to symptoms which vary depending on the site of lodgment of the cysticerci and host response. The symptoms may take months to years before manifesting after infection is acquired. The cysticercosis may involve skin or subcutaneous tissue or less commonly eyes, lungs, liver and spinal cord, etc. Involvement of brain, i.e., neurocysticercosis is a serious complication of this infection. This is discussed in detail elsewhere in the book.

Diagnosis

Microscopic examination of the stool may demonstrate the eggs of *Taenia* (**Fig. 4**), but species cannot be identified from the eggs.

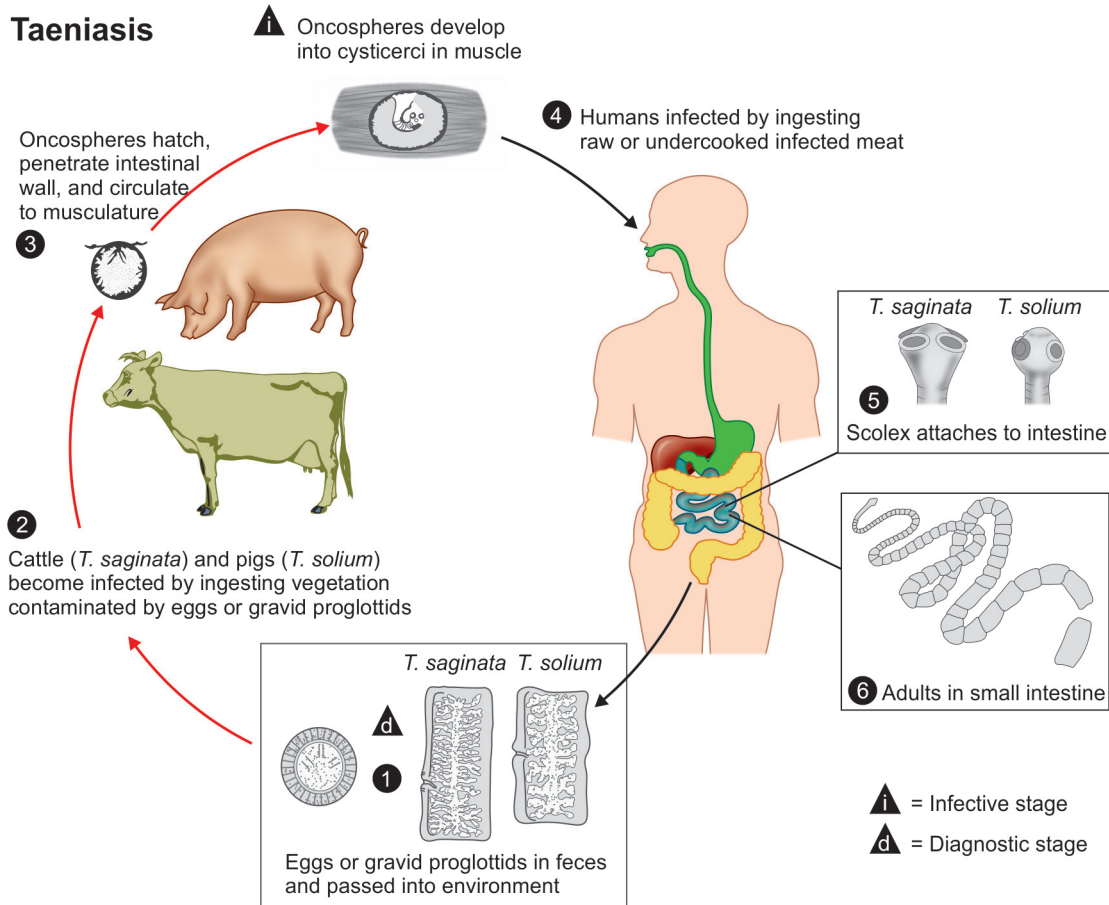


Figure 3 Life cycle of *Taenia*

Source: Public Health Image Library (PHIL), CDC, USA.

Species can be identified only on examination of the proglottids, pressed between two microscopic slides and using a hand lens. Available serologic tests are not helpful in diagnosis of intestinal infection. DNA based differentiation between the two species (i.e., *solium* and *saginata*) has been tried using probes, polymerase chain reaction (PCR) with species specific primers and PCR followed by restriction enzyme analysis (PCR-REA), but are also only of research value. The Tso31 nested PCR in stool samples has been found to be sensitive and specific. Tissue cysticercosis can be diagnosed by biopsy of the tissue which shows the scolex with suckers and hooks. Ocular cysticercosis can be diagnosed by ophthalmoscopy.

Treatment and Prevention

Praziquantel is an effective drug for treatment. It is used as a single oral dose of 5–10 mg/kg. Niclosamide can also be used as single dose therapy in dose of 50 mg/kg oral dose. Nitazoxanide has been found to be effective in children not responding to praziquantel and niclosamide. Purgatives can be given with praziquantel to expel out the dead worm, otherwise it gets absorbed after being killed. Proper sanitation, good animal rearing practices and proper sewage disposal measures are effective in preventing infection. Pork should be carefully examined and consumed after adequate cooking.

TAENIA SAGINATA (BEEF TAPEWORM)

This tapeworm is also known as beef tapeworm as cattle act as the intermediate host. The life cycle, pathogenesis, clinical features and treatment of *T. saginata* are similar to that of *T. solium*. The infection



Figure 4 Egg of *Taenia* sp. under high magnification of 400X
Source: Public Health Image Library (PHIL), CDC, USA.

occurs by ingestion of raw or under cooked beef. Human infection is not possible with ingestion of eggs and no tissue cysticercosis occurs. Diagnosis is made by examining the proglottids and can be differentiated from those of *T. solium* by counting the number of lateral uterine branches in the gravid segments. The count in the segments of *T. saginata* is more than 13 and that in *T. solium* is less than 13.

DIPHYLLOBOOTHRIUM LATUM (FISH TAPEWORM)

Disease caused by infection with *Diphyllobothrium latum* is seen in parts of Europe, Japan and North America. Rare cases have been reported from Indian Subcontinent.

Etiology

This is the longest tapeworm to infect man. Man is the definitive host and the parasite has two intermediate hosts. The adult worm sheds up to a million eggs each day which are passed in the stools of infected children. The eggs are not infective to humans. When these eggs reach fresh water due to contamination with human feces, they hatch into first stage larva (coracidium). These larvae are ingested by crustaceans (*Cyclops*) which are the first intermediate hosts. These *Cyclops* are in turn eaten by fresh water fish which act as the second intermediate host. Here they transform into the second stage larva (proceroid larva). Consumption of raw or improperly cooked fish by children leads to infection. Life cycle is depicted in **Figure 5**.

Pathogenesis

Diphyllobothrium latum competes with the host for vitamin B₁₂ in the ileum and also interferes with its absorption from the diet. There is also parasite mediated dissociation of the vitamin B₁₂-intrinsic factor complex in the gut. This interference with vitamin B₁₂ is racially determined and commonly seen in Finland. It is also postulated that the strains found in Finland absorb more vitamin B₁₂ than strains elsewhere.

Clinical Features

Nonspecific abdominal symptoms are seen in children. They may complain of loss of appetite, vomiting, fatigue, weakness and weight loss. Megaloblastic anemia is the only significant clinical manifestation (bothriocephalus anemia). Vitamin B₁₂ levels may be low in many infected children, but clinically significant anemia is seen in very few ($\approx 2\%$). Other features of megaloblastic anemia like leukopenia, thrombocytopenia, signs of peripheral neuropathy and degeneration of the posterior column of spinal cord are also present. The anemia becomes more significant in children with other co-existing causes of megaloblastic anemia.

Management

Diagnosis can be easily made by examination of the stool for eggs. The eggs are found in abundance in stool of infected children and are different from eggs of other tapeworms. Praziquantel is the drug of choice in a single oral dose at 5–10 mg/kg. Niclosamide is also an effective drug. Vitamin B₁₂ deficiency improves with the treatment of infection and supplementation with the vitamin. The disease can be prevented by improved sanitation and consumption of properly cooked fish. Freezing fish at -20°C for 7 days also kills the larva and prevents infection.

ECHINOCOCCUS GRANULOSUS (DOG TAPEWORM)

This zoonosis is one of the exceptions where humans are not the definite host. Humans act as intermediate hosts and the disease

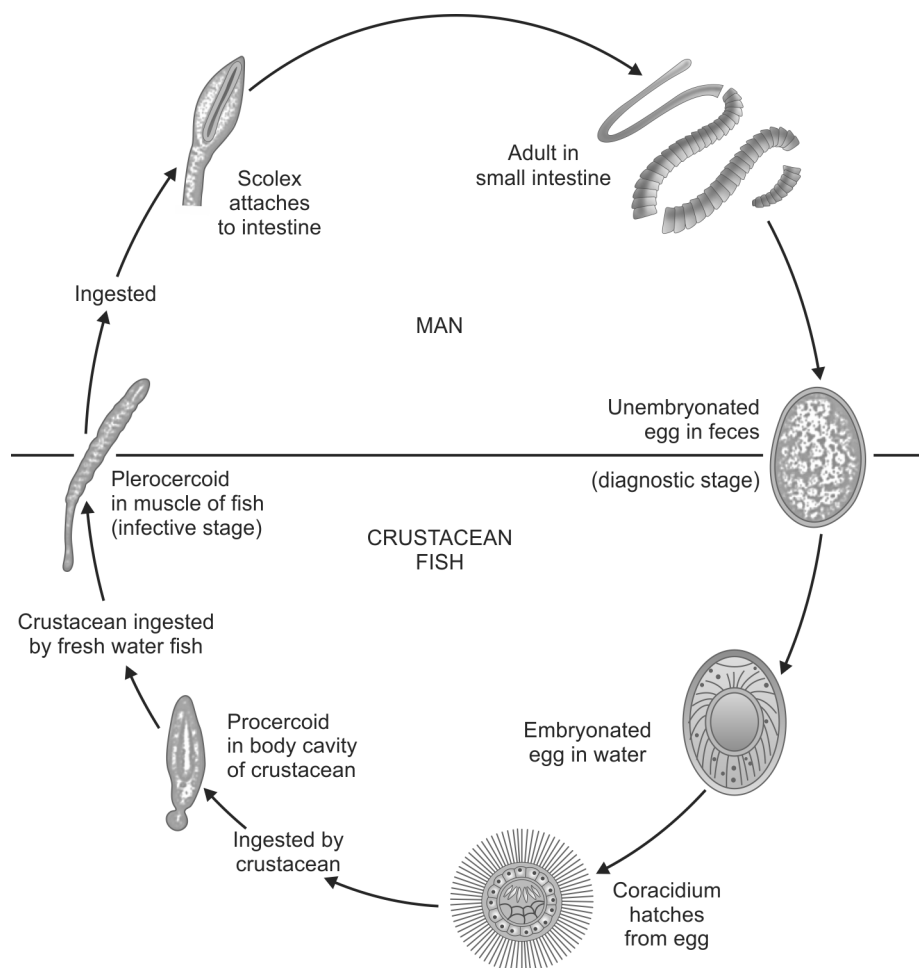


Figure 5 Life cycle of *Diphyllobothrium latum*
Source: Public Health Image Library (PHIL), CDC, USA.

caused is known as cystic hydatid disease. Other members of the *Echinococcus* species are *E. multilocularis* which causes alveolar echinococcosis and *E. oligarthrus* causes polycystic echinococcosis. Details are in the next chapter.

HYMENOLEPIS NANA (DWARF TAPEWORM)

It is a very common infection among children spread by feco-oral route. It is the only cestode which does not require an intermediate host. It is very small in size (≈ 2 cm) and thousands of these worms inhabit the intestines of the host. Usually causes no symptoms or minor symptoms like abdominal pain and anorexia. Diagnosis is by demonstration of eggs (**Fig. 6**) in stools. Drugs used for treatment are praziquantel and nitazoxanide.

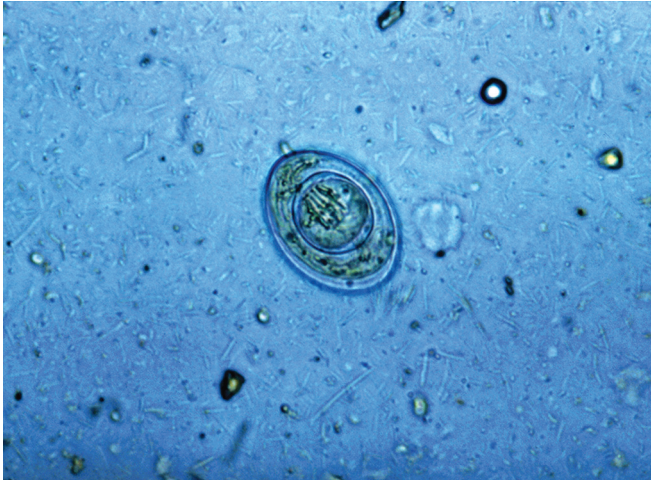


Figure 6 Egg of *Hymenolepis nana*
Source: Public Health Image Library (PHIL), CDC, USA.

IN A NUTSHELL

1. Tapeworm diseases are common in humans, especially in children. The infection is seen all over the world.
2. Transmission of infection occurs by feco-oral route (tissue cysticercosis) or by ingestion of raw or poorly cooked meat or fish (adult worm).
3. Most of the adult worm infection causes no significant symptoms.
4. Infection by larval stage can cause serious manifestations like neurocysticercosis and echinococcosis.
5. Intestinal infections are easy to treat. Infection by larvae also responds well to drugs where the drugs need to be given for a longer duration.
6. Prevention of infection is possible by improving standard of hygiene, provision of safe drinking water and proper inspection and cooking of meat.

MORE ON THIS TOPIC

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Chapter 32.16

Hydatid Disease: Echinococcosis

SK Gupta

Hydatid disease is a parasitic infestation caused most commonly by *Echinococcus granulosus* tapeworm. The other responsible species are *Echinococcus multilocularis* and *Echinococcus vogeli*. The disease is endemic in many sheep and cattle raising countries such as Australia, Africa, Middle East and Latin American countries. However, the disease has spread to non-endemic regions also and has become a global health problem. Man is an accidental host and a *dead-end* for the parasite.

LIFE CYCLE

Echinococcus granulosus is a cestode, the adult form of which is 3–6 mm long and resides in the small intestine of the definitive host. The definitive hosts are usually dogs and other canines. The gravid proglottids present in the definitive host release eggs which pass into their feces. These eggs, then ingested by the intermediate host such as cattle, sheep, goat, etc., release an oncosphere larva in the small bowel of the intermediate host which penetrates the intestinal wall and enters the blood or the lymph vessels. It can then reach various organs particularly the liver (which acts as the first filter) and the lungs (the second filter). On reaching these organs, the oncosphere larva develops into the hydatid cyst (metacestode larvae). The hydatid cyst has two layers, the inner nucleated germinal layer known as the endocyst and an outer acellular layer called the ectocyst. The ectocyst is in turn surrounded by a host derived fibrous layer called the pericyst. The germinal layer gives rise to brood capsules and protoscolices. The brood capsules can detach from the germinal layer and give rise to daughter cysts that fill the cyst cavity. The definitive hosts get infected by eating the offal of the intermediate host which contains viable protoscolices. After ingestion, the protoscolices evaginate and attach to the canine intestinal mucosa. They attain the adult stage (sexual maturity) in 4–6 weeks.

Human beings are an accidental host and a *dead-end* for the parasite. They get infected by coming into contact with infected dogs, the mode of transmission being through the fecal-oral route. *Echinococcus multilocularis* has a similar life cycle with the difference that definitive hosts are fox and to lesser extent dogs, coyotes and wolves and the intermediate hosts are small rodents.

PATHOGENESIS

The disease mostly affects the liver in adults but in children pulmonary hydatidosis is more common. Combined lung and liver involvement is more common in children than in adults. Hydatid disease can affect almost any organ in the human body and consequently has myriad presentations depending upon the organ of involvement. Since it is a slow growing disease, it is usually asymptomatic in the initial phase and by the time symptoms manifest the hydatid cyst has grown to a considerable size. It is important to be aware of this disease because it forms the differential diagnosis of space occupying lesion in many organs. It is usually amenable to a combination of surgical and medical treatment but can recur and at times can be life-threatening.

CLINICAL FEATURES

The initial phase of primary infection is almost always asymptomatic. The small cysts which are formed initially remain

asymptomatic for many years and become symptomatic only when they become large. Hydatid disease is usually diagnosed in adult patients because of the slow growing nature of hydatid cyst (ranging from 1 cm to 5 cm in diameter per year). Only 10–20% of cases are diagnosed in patients younger than 16 years of age.

Cerebral and ocular hydatid cysts can become symptomatic even when they are small in size hence most cases of cerebral and ocular echinococcosis are diagnosed in the pediatric age group. Symptoms can also be precipitated if the cysts rupture as the hydatid cyst fluid is allergenic and may cause anaphylaxis. Apart from the liver and lungs, hydatid disease can affect almost any organ which includes (but not limited to) brain, eyes, heart, kidney, spleen, pancreas, salivary glands, breast, bone and muscles. The clinical presentation would therefore depend upon the organ of involvement, the size of the cyst, the mass effect within the organ and upon surrounding structures and complications relating to cyst rupture and secondary infection.

Liver Hydatid Disease

It usually presents as pain in the right upper quadrant with or without jaundice. The child may also complain of nausea and vomiting. There may be a history of fever if the cyst gets infected. In large hydatid cysts, abdomen may be distended and there is a palpable liver which is usually smooth, firm and non-tender. Sometimes a liver hydatid cyst may mimic a palpable gall bladder. If the cyst ruptures intraperitoneally, allergic reaction ranging from mild anaphylaxis to a fatal reaction can be precipitated. Multiple intraperitoneal hydatid cysts (presenting as multiple palpable abdominal lumps) can result from rupture of liver hydatid cyst. More commonly, these patients present as acute abdomen with abdominal pain, vomiting, distension and absent bowel sounds. In such cases, it is difficult to differentiate it from ruptured liver abscess. A detailed and thorough clinical history will usually provide clues to the diagnosis. The liver hydatid cysts can also rupture into the biliary tree leading to cholangitis and/or biliary obstruction by daughter cysts.

Pulmonary Hydatidosis

It presents with cough, mucopurulent sputum, fever, chest pain and dyspnea. Hemoptysis is another presenting symptom. These are more common in males than in females and can be unilateral or bilateral. The right lung is more commonly involved. In the lungs, ruptured cyst membranes may be expectorated out through a broncho-pulmonary fistula or can be retained to act as a nucleus for bacterial or fungal infection. Rupture of hydatid cyst can result in dissemination of protoscolices leading to multiple secondary echinococcosis. Alveolar echinococcosis (caused by *Echinococcus multilocularis*) usually presents later than the cystic form. They have an initial asymptomatic period ranging from 5 years to 15 years followed by a chronic form. If left untreated they have high mortality rate.

A diagnosis of hydatid disease should be kept as a possibility in the presence of a cystic mass in a person with history of exposure to sheep or dogs in areas where *Echinococcus granulosus* is endemic. These must be differentiated from benign cysts, abscesses, cavitory tuberculosis, fungal infection and benign or malignant neoplasms.

INVESTIGATIONS

The diagnosis of hydatid disease can mostly be established by the combined use of noninvasive radiological imaging and immunodiagnostic tests. Eosinophilia, which was also considered to be of value in the diagnosis of hydatid disease, is positive in less than 25% of infected persons.

Imaging

The most commonly used imaging modality for the diagnosis of hydatid disease of the liver is abdominal ultrasonography. It gives an accurate delineation of the site, size and number of hydatid cysts. It also gives a reasonably accurate assessment of the vitality of the hydatid cyst. The World Health Organization (WHO) has developed a classification system for hepatic cysts identified by ultrasonography (**Box 1**).

CT scan is the modality of choice for pulmonary and cerebral hydatidosis, whereas MRI is the preferred imaging modality for hydatid cysts involving the muscles, salivary glands and retroperitoneum. CT abdomen is also helpful in more accurate localisation of liver hydatid cysts in relation to the segmental anatomy of the liver.

Serology

Antibody assays are useful to confirm diagnosis in patients with presumptive radiological diagnosis even though a fair number of patients with cystic echinococcosis will not have a detectable immune response. Hepatic cysts are more likely to demonstrate a positive immunological test than the pulmonary hydatid cysts. The likelihood of a positive serological test is inversely related to the degree of sequestration of echinococcal antigens within the cyst cavity. Thus, intact cysts are unlikely to demonstrate a positive immune reaction, whereas cysts that have previously ruptured or leaking cysts will have a positive immunological test. Amongst the various immunological tests described, Casoni's test which is a type of immediate hypersensitivity reaction is positive only in approximately 60% of cases. It is also falsely positive in other parasitic infections. The indirect hemagglutination test is sensitive, but enzyme linked immunosorbent assay (ELISA) is more accurate and is the preferred diagnostic test for initial screening. Specific echinococcal antigens can be demonstrated by immunoblot assays but are not commonly used.

Aspiration

In seronegative individuals, percutaneous aspiration of the cyst under ultrasonographic guidance and the demonstration of protoscolices or hydatid membranes are confirmatory. This test is associated with a small risk of anaphylaxis and the need to treat such a reaction should be anticipated. It is also advisable to start anthelmintic treatment before carrying out the aspiration. In patients with pulmonary hydatidosis, protoscolices can be demonstrated in sputum or bronchial washings.

TREATMENT

Till the 1980s, surgery was considered to be the only modality for treatment of echinococcal cysts. However availability of more efficacious anthelmintic treatment with newer benzimidazole compounds have supplemented and in some cases replaced

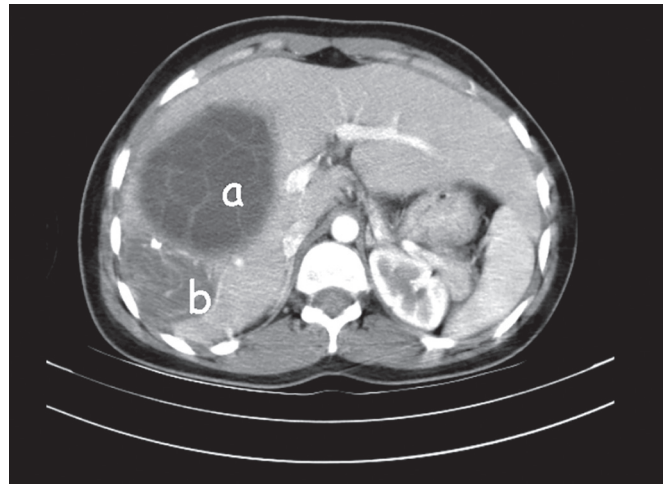


Figure 1 CT abdomen showing two hydatid cysts in the liver, (a) cyst showing honeycomb appearance (b) cyst with calcification of walls
Source: Dr Pankaj Kamra, MD, Consultant Radiologist, Allahabad.

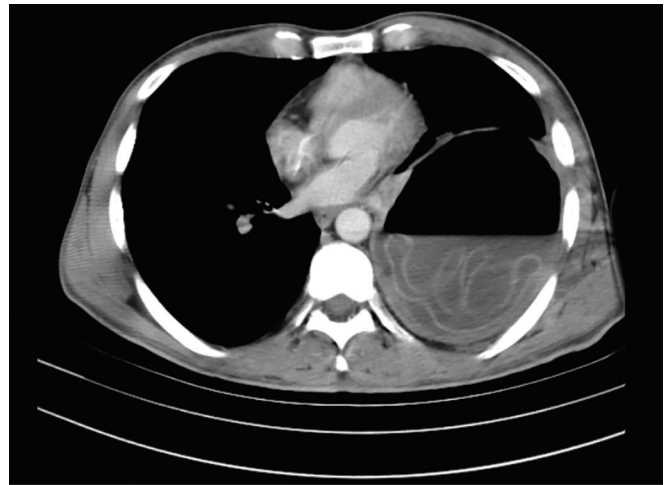


Figure 2 Hydatid cyst showing the typical water lily sign and air fluid level
Source: Dr Pankaj Kamra, MD, Consultant Radiologist, Allahabad.

surgical treatment. More recently, treatment with percutaneous cyst aspiration, injection of scolical agents and re-aspiration (PAIR) has been introduced with success. The various treatment options have been reviewed by the WHO Informal Working Group on Echinococcosis (**Table 1**).

Surgery

Complete surgical removal of the intact hydatid cyst is the definitive treatment resulting in complete cure (**Figs 3 and 4**). The aim of surgery is complete removal of the cyst without spilling the cyst contents and is best achieved by pericystectomy. The plane of surgical resection lies between the ectocyst (the outer layer of the hydatid cyst) and the pericyst (which is the layer of compressed host tissue). Other surgical procedures such as simple drainage, capitonnage, marsupialization (de-roofing) and resection of the involved organ may be used depending upon the location of the cyst. A more radical surgical procedure is associated with a higher operative risk but a lesser likelihood of recurrence and *vice-versa*. Whenever lesser surgical procedures are being used, adjunctive anthelmintic treatment should always be given. Surgery is the

BOX 1 WHO Classification for hepatic hydatid disease

- CL—Unilocular cysts with uniform anechoic content (but without any pathognomonic signs)
- CE1—Unilocular cyst with uniform anechoic content but with the presence of pathognomonic signs such as visible cyst wall and snowflake sign
- CE2—Multivesicular, multiseptated cysts (**Fig. 1**)
- CE3—Anechoic content with detachment of laminated membrane from the cyst wall visible as a floating membrane or *water-lily sign* (**Fig. 2**)
- CE4—Heterogeneous hypo- or hyper-echoic degenerative content without any visible daughter cysts
- CE5—Cysts characterized by thick calcified wall producing a cone-shaped shadow. The calcification may be partial or total.

TABLE 1 Treatment of hydatid cyst according to the WHO staging

WHO staging	Ultrasound picture	Treatment
CE1	Uniformly anechoic cyst with fine echoes settled representing hydatid sand	<5 cm Albendazole alone >5 cm Albendazole + PAIR
CE2	Multiseptate honeycomb cyst	Surgery + Albendazole
CE3	Cyst with detached membranes	<5 cm Albendazole alone >5 cm Albendazole + PAIR
CE4	Cysts with heterogeneous hypo/hyperechoic contents and no daughter cysts	Wait and watch
CE5	Solid and calcified walls	Wait and watch

preferred treatment for large liver cysts (> 10 cm in diameter), if the cysts are secondarily infected, or if they are located in certain organs such as lung, kidney or brain.

There is a definite risk of anaphylaxis during surgical intervention and can be minimized by instilling scolicalidal agents in the cyst cavity intraoperatively. These include 10% formaldehyde, 3% hypertonic saline and 10% povidone-iodine. Formaldehyde is not used nowadays because of the risk of severe sclerosing cholangitis if cyst-biliary communications are present. It is also prudent to pack the abdominal contents by pads soaked in 10% povidone-iodine to prevent dissemination of the protoscolices during surgery. Surgery is contraindicated in patients who are at poor surgical risk or have multiple cysts that are difficult to access. Operative mortality ranges from 0.5% to 4% and is higher in patients undergoing reoperations.

Chemotherapy

Anthelmintic treatment with benzimidazole compounds can be used as the sole modality of treatment in simple hydatid cysts less than 1 cm in diameter or as an adjunct to surgery. Nearly a one-third of the patients so treated demonstrate a complete and permanent disappearance of the cyst while nearly 50% show a significant reduction in the cyst size. However, nearly 20–40% of patients do not show a favorable response. Medical treatment is not useful in complicated multiseptated cysts or cysts with thick and calcified cyst wall. Both albendazole (10–15 mg/kg/day) and mebendazole (40–50 mg/kg/day) have been used with good results. Albendazole is better than mebendazole because of its better absorption from the intestine and penetration into the cyst cavity. The minimum duration of treatment is 3 months. Adverse reactions in the form of neutropenia, hepatotoxicity, alopecia, etc., can occur but these are reversible. Pregnancy, chronic liver disease and bone marrow depression are contraindications for medical treatment. Praziquantel has also been used in different regimens (50 mg/kg daily, once weekly, or once every two weeks). A combination of praziquantel plus albendazole is superior to albendazole alone.

PAIR

It consists of Percutaneous puncture (under sonographic guidance), Aspiration of the cyst contents, and Injection of scolicalidal agent (95% ethanol or hypertonic saline) for at least 15 minutes and Re-aspiration (PAIR). This is a relatively newer option for the treatment of hydatid cysts particularly those of the liver. This technique is useful for patients with smaller cysts and for those who either cannot undergo or refuse surgery. PAIR is contraindicated for inaccessible or superficially located liver cysts

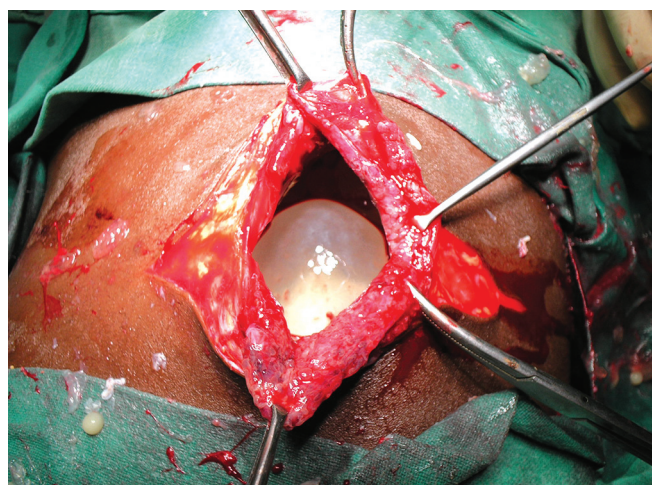


Figure 3 Operative photograph showing a daughter cyst within the opened cyst cavity in the liver

Source: Professor AN Gangopadhyaya, Department of Pediatric Surgery, Institute of Medical Sciences, BHU, Varanasi.

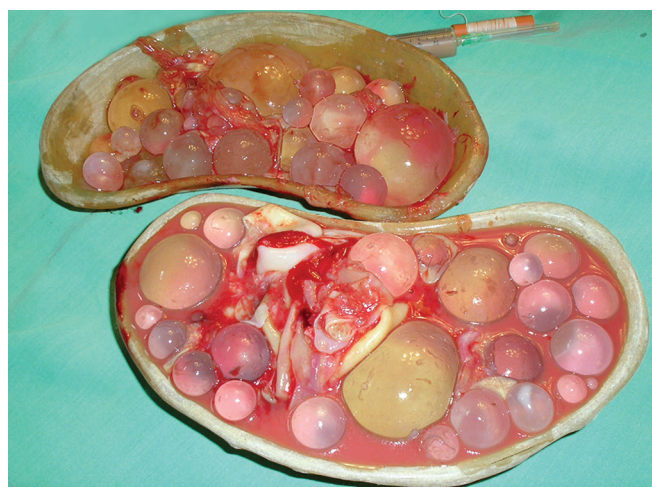


Figure 4 Operative photograph showing multiple daughter cysts evacuated from a liver hydatid cyst

Source: Professor AN Gangopadhyaya, Department of Pediatric Surgery, Institute of Medical Sciences, BHU, Varanasi.

and for inactive or calcified cystic lesions. It is best used for single or multiple cysts in the liver, spleen, kidney and the abdominal cavity. In view of the risk of sclerosing cholangitis, PAIR should not be used in liver cysts with cyst-biliary communication as evidenced by presence of bilirubin in the cyst fluid or by endoscopic retrograde cholangiopancreatography (ERCP) and/or operative cholangiogram. It is preferable to do PAIR under anthelmintic coverage which should be continued for at least one month after the procedure. A meta-analysis of PAIR combined with anthelmintic treatment has shown better clinical efficacy, lower morbidity and mortality and a shorter hospital stay than surgery.

Follow-up

Objective response to treatment is best assessed by ultrasonography, computed tomography or magnetic resonance imaging. These should be done at intervals of 3 months and should be continued for at least 3 years.

PREVENTION AND CONTROL

The earliest successful control program was launched in Iceland and resulted in eradication of the disease. Health education which led to elimination of home slaughter of sheep was the sheet anchor of this program. Similar programs based on education of rural populations and prohibition of farm slaughter (backed by legislative action) were initiated in New Zealand and Tasmania and resulted in the gradual elimination of transmission.

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IN A NUTSHELL

1. Hydatid disease is a zoonoses caused by the cestode tapeworm, *Echinococcus granulosus* and *Echinococcus multilocularis*.
2. Man is an accidental host and gets infected by the fecal-oral route while coming in contact with infected dogs and sheep.
3. Hydatid disease can affect almost any organ of the body. However, liver and lungs are the most commonly affected organs.
4. Hydatid cysts are slow growing and usually present late. Clinical features depend upon the location, size and nature of the cyst.
5. Noninvasive imaging modalities combined with immunological tests are diagnostic.
6. Surgery is the mainstay of treatment for the vast majority of hydatid cysts. Medical treatment is a necessary adjunct of surgical treatment and can be used as the sole modality for simple, isolated cysts.
7. PAIR is a relatively newer technique which has shown better results than surgical treatment in cases of hydatid cysts of the liver and other intra-abdominal organs.

Chapter 32.17

Schistosomiasis

Ritabrata Kundu, Devdeep Mukherjee

Schistosomiasis (bilharziasis) is a parasitic disease caused by trematode worms of the genus *Schistosoma*. Humans are primarily affected by five species: *Schistosoma mansoni*, *Schistosoma japonicum*, *Schistosoma haematobium*, *Schistosoma intercalatum*, and *Schistosoma mekongi*.

EPIDEMIOLOGY

Although not commonly seen in India, Schistosomiasis remains a major cause of mortality for the developing regions of Africa, South America, the Caribbean and the Middle East. In Asia, it is more commonly seen in Cambodia and Laos. Globally, it is the third highest cause of morbidity after malaria and intestinal helminthiasis. Schistosomiasis is endemic in 74 countries. World over, almost a billion people are at risk of infection and close to 300 million people are infected with the parasite. The disease burden is contributed by the three major species affecting humans (*S. mansoni*, *S. haematobium*, and *S. japonicum*). It is estimated to be close to 25 million DALY (disability adjusted life years). The disease is more commonly seen in developing countries having areas with poor hygiene. Children bathing or swimming in water contaminated with the infective stage of the parasite (cercariae) are more commonly at risk.

LIFE CYCLE

The life cycle involves humans or animals as the definitive host and a snail as an intermediate host. The definitive host gets infected on exposure to cercariae contaminated fresh water (Fig. 1).

Sexual phase Cercariae penetrate through the host skin by releasing glandular secretions, lose their tails and transform into schistosomula (young schistosomes). After two days, the schistosomula penetrate through the dermis and then the endothelium of blood vessel to be carried to the lungs where they may reside for many days. Finally they reach the liver and begin feeding on red blood cells. They undergo maturation and mate within the liver vessels and finally come out as male and female worms and penetrate more commonly the portal or the pelvic vessels. The only exception is *S. haematobium*, which penetrates the urinary bladder venous plexus. The females lay eggs within the blood vessels they inhabit. The eggs are carried within the blood vessels to the liver where they are lodged within the presinusoidal portal venules. Few eggs may reach the intestines and are passed with feces (Fig. 2). Eggs of *S. haematobium*, however reach the urinary bladder and are passed with urine.

Asexual phase The eggs hatch into miracidia (ciliated larval forms) on coming in contact with water. This miracidia then enters the snail where it transforms into cercariae to complete the asexual phase of development. The cercariae are finally released to complete the life cycle.

CLINICAL FEATURES

The clinical features mainly depend on the site of infection by the parasite. However, it can be broadly classified into an acute form and a chronic form of the disease. *Acute* (Katayama syndrome) disease occurs within a few weeks of infection; *Chronic* (most common form) may manifest after months or years after infection.

Katayama Syndrome

A serum sickness like syndrome, whereby antigens are liberated and cause a T helper type 1 cell mediated inflammatory response along with the liberation of several interleukins (IL-1 and IL-6) and tumor necrosis factor (TNF). Clinical features include fever,

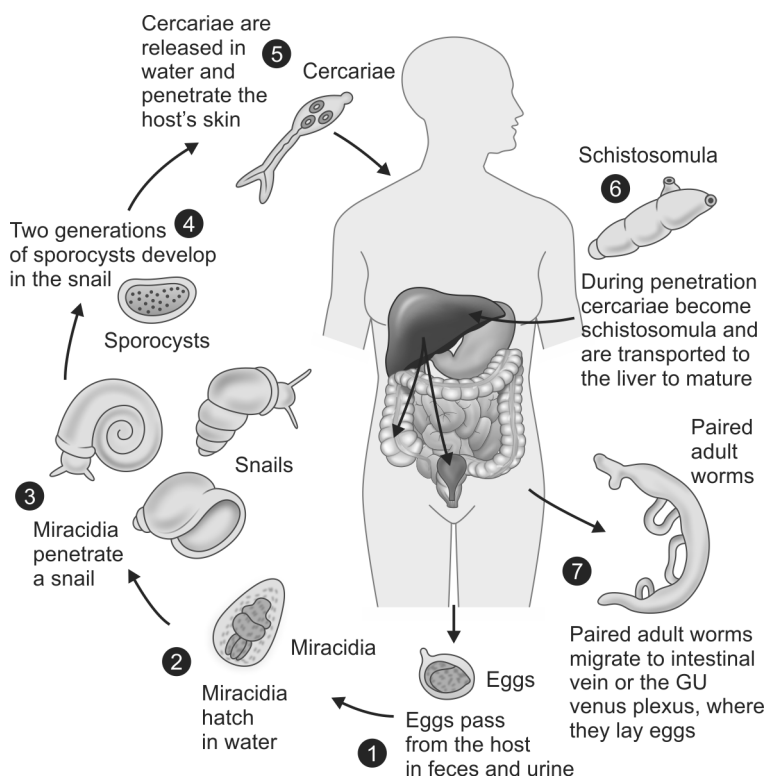
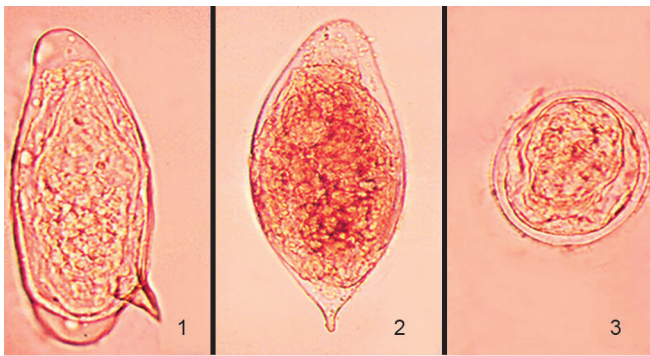


Figure 1 Life cycle of *Schistosoma*

Source: Public Health Image Library (PHIL), CDC, USA.



1. *Schistosoma mansoni* 2. *Schistosoma haematobium* 3. *Schistosoma japonicum*

Figure 2 Eggs of *Schistosoma*

Source: Public Health Image Library (PHIL), CDC, USA.

malaise, cough, generalized body ache, abdominal pain, blood in stool, and an erythematous, maculopapular rash. The symptoms may resolve spontaneously in a few weeks without treatment. However it is extremely imperative to treat these patients to prevent them from developing chronic schistosomiasis.

Chronic Schistosomiasis

Following inadequate treatment, the parasites may remain in the body resulting in chronic schistosomiasis. A T helper type 2 cell mediated granulomatous reaction along with the liberation of interleukins (IL-4, IL-5, IL-13) and cytokines result in fibrosis of tissues. Type 1 T helper (Th1) cells also has a role in granuloma formation. The immunological reaction causes organ injury but fails to destroy the parasites. Manifestations depend on the site of invasion by parasite:

Gastrointestinal Abdominal pain, dysentery, hepatomegaly, periportal fibrosis, splenomegaly, ascites, prominent abdominal blood vessels, esophageal varices and portal hypertension.

Urogenital Cystitis, dysuria and hematuria are commonly seen. In advanced cases we may see damage to the kidneys, ureters and bladder. Genital lesions are common and patients may develop irreversible infertility. Co-infection with HIV hastens the progression of the viral infection. *S. haematobium* is also notorious for causing squamous cell carcinoma of the urinary bladder.

Heart and lungs Persistent cough, hemoptysis, wheeze and breathlessness may occur following infection.

Central nervous system Patients may complain of headache and dizziness. Lumbosacral myelopathy characterized by loss of power and sensation in lower limbs is seen. Convulsions can also occur. Patients may simply present with a space occupying lesion in the brain or spinal cord. Neurological involvement is reported in 5% of cases.

LABORATORY INVESTIGATIONS

Stool and Urine

Stool (for *S. mansoni*, *S. japonicum*, *S. mekongi* and *S. intercalatum* eggs) or urine samples (for *S. haematobium* eggs) are examined microscopically for parasite eggs. These are the gold standard investigations to diagnosis Schistosomiasis. The eggs of *S. mansoni*, *S. japonicum*, *S. mekongi*, and *S. intercalatum* are shed with stool. These can be detected by the Kato-Katz technique or the Ritchie technique. Eggs of *S. haematobium* are shed in urine. Routine urine examination will show evidence of hematuria. Diagnosis of *S. haematobium* can be performed by filtration technique using paper, nylon or polycarbonate filters.

Serologic Tests

Since the eggs are shed infrequently and in small amounts, it is at times necessary to establish the diagnosis by serologic testing. It is especially essential for people living in nonendemic regions and in areas of low transmission. This test helps in identifying exposure to infection and also guides on extent of treatment required.

Antigen Detection Methods

Advances have been made in isolating antigens of parasites from the body. Monoclonal antibodies have been used to detect parasite antigens in blood and urine. Few other antigen detection methods are the circulating anodic antigen (CAA) and circulating cathodic antigen (CCA).

Antibody Detection Methods

Serum samples are examined by FAST-ELISA using *Schistosoma mansoni* adult microsomal antigen (MAMA). A reaction greater than 9 units/ μ L serum is termed positive for infection with *Schistosoma* species. The sensitivity of the above test however declines for species apart from *S. mansoni*. Immunoblots of *S. haematobium* and *S. japonicum* can be utilized for diagnosis.

TREATMENT AND PREVENTION

Praziquantel is the drug of choice. Efficacy is however dependent on dose: 60 mg/kg/day in 3 divided doses for *S. japonicum*, *S. mekongi*; and 40 mg/kg/day in 2 divided doses *S. mansoni*, *S. haematobium*, *S. intercalatum*. Duration of treatment is for 1–2 days.

Artemisinin derivatives (artesunate and artemether) have been used for prevention. Several doses when administered at weekly or bi-weekly intervals result in increasing the protection rates as a result of its killing of juvenile schistosomula. The combination of praziquantel and artesunate have a greater protection rate against Schistosomiasis.

IN A NUTSHELL

1. Schistosomiasis is caused by trematode worms of the genus *Schistosoma*. Humans are primarily affected by five species: *Schistosoma mansoni*, *Schistosoma japonicum*, *Schistosoma haematobium*, *Schistosoma intercalatum*, and *Schistosoma mekongi*.
2. It has an acute and a chronic (more common) course.
3. Isolated commonly through urine and stool specimens.
4. School going children are more at risk following swimming in parasite infested water or drinking water contaminated with cercariae.
5. Praziquantel is the drug of choice.

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Section 33 FUNGAL INFECTIONS

Section Editor Piyush Gupta

Chapter 33.1

Fungi

VG Ramachandran, Piyush Gupta

Out of about 100,000 species of fungi, approximately 200 or so are known to cause infection in man and animals. Fungal infections are also known as *mycoses*. Mycoses are recognized less frequently than bacterial, viral, and parasitic infections but constitute a significant cause of morbidity and mortality worldwide. Some of the fungi are geographically restricted but majority are found globally. Fungal diseases are known to occur as localized outbreaks but have not been reported in the form of an epidemic.

In recent times, fungi have emerged as important agents of opportunistic infections. The compromised host is at increased risk of severe systemic mycotic infections as a result of congenital or acquired immune deficiencies, malignancies, metabolic disorders, and following transplantation or chemotherapy. Increased life expectancy has had its fall-out, with aged patients being more susceptible to secondary fungal infections than the younger individuals.

Mycoses are primarily acquired and classified as cutaneous, mucocutaneous and pulmonary with respect to their site of infection. They are usually not transmitted from person to person except the dermatophytoses. Fungal infections are also not sexually transmitted with the exception of candidal balanoposthitis and rarely blastomycosis and histoplasmosis.

Some fungi are toxic and their ingestion may result in serious clinical manifestations (mushroom poisoning or mycetismus). Some other fungi produce toxins such as aflatoxin, muscarine,

rubratoxin, etc. Some fungal species act as allergens and cause allergic manifestations. **Table 1** lists a few of the common fungal infections and their causative organisms.

MORE ON THIS TOPIC

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Table 1 Common fungal infections and their causative organisms

Type of mycoses	Disease	Causative fungi
Superficial	Pityriasis versicolor, Dermatophytoses (<i>Tinea capitis</i> , <i>T. barbae</i> , <i>T. corporis</i> , <i>T. cruris</i> , <i>T. unguum</i> , <i>T. pedis</i> , etc.)	<i>Malassezia furfur</i> <i>Trichophyton</i> , <i>Microsporum</i> , <i>Epidermophyton</i>
Subcutaneous	Mycetoma	<i>Madurella</i> , <i>Phialophora</i> , <i>Actinomadura</i>
Systemic	Chromoblastomycosis Phaeohyphomycosis Rhinosporidiosis Histoplasmosis Blastomycosis Coccidiomycosis	<i>Cladosporium</i> , <i>Exophiala</i> , <i>Fonseceae</i> <i>Wangiella</i> , <i>Exophiala</i> <i>Rhinosporidium</i> <i>Histoplasma capsulatum</i> <i>Blastomyces dermatidis</i> <i>Coccidioides immitis</i>
Opportunistic	Candidiasis Cryptococcosis Aspergillosis Zygomycosis Trichosporonosis	<i>Candida spp.</i> <i>Cryptococcus</i> <i>neoformans</i> <i>Aspergillus spp.</i> <i>Rhizopus</i> , <i>Mucor</i> <i>Trichosporon</i>

Chapter 33.2

Antifungal Therapy

Arunaloke Chakrabarti, Prashant Sood

Medical advancements in neonatology, pediatric immunodeficiency disorders, hematology, oncology and transplantation have substantially reduced the mortality and morbidity in children. These advancements are intimately linked with widespread use of antibiotics, immunomodulators including steroids and invasive technologies. These strides in pediatric practice and in general modern medicine have given rise to a growing population of children highly vulnerable to invasive and noninvasive fungal infections. There has been a 307% rise in fungal infection burden in adults and children between 1979 and 2000. Fortunately, antifungal development has kept pace with their growing need. This is all the more pertinent because fungi are eukaryotic microorganisms with several biosynthetic and genetic similarities with humans. This poses a formidable challenge to exploit fungus-specific metabolic differences for devising antifungals. Last two decades have witnessed the arrival of highly effective second and third-generation azoles and echinocandins. Several new antifungals including nikkomycins, sordaricins, new generation triazoles and echinocandins are also in the pipeline.

Pediatric patients are not just *little adults*. Compared to adults, they display significant differences in host biology, predisposition, epidemiology and presentation of fungal infections, and pharmacokinetics and pharmacodynamics of antifungal agents. Furthermore, neonates and young infants comprise an entirely unique population. Despite the arrival of several effective antifungals, very few clinical trials have evaluated their pharmacology, clinical safety and efficacy in pediatric age groups. Thus, of the 14 antifungal classes, only a handful are approved for pediatric use, largely based on extrapolated pharmacokinetics data from adults. Even these are often under-dosed and incorrectly prescribed by clinicians due to incomplete understanding of antifungal pharmacology in children. This chapter provides succinct details of current understanding and treatment standards of antifungals approved for pediatric use.

POLYENES

Pharmacology, Spectrum and Resistance

Polyenes comprise of amphotericin B deoxycholate and three lipid formulations including amphotericin B lipid complex (ABLC), amphotericin B colloidal dispersion (ABCD) and liposomal amphotericin B (LAMB). Amphotericin B preferentially binds to fungal ergosterol forming *micropores* in the cell membrane. These pores disrupt fungal cell osmotic integrity, causing leakage of intracellular potassium and magnesium, thereby killing the fungal cell. Additional immune-adjuvant actions include oxidation-dependent stimulation of macrophages, immune cell proliferation, and upregulation of IL-1 β , TNF- α , IL-1RA, IL-12, IFN- γ and nitric oxide production. Amphotericin B lipid formulations have significantly better therapeutic index, selective tissue distribution and lower nephrotoxicity.

Amphotericin B

Amphotericin B is a broadspectrum antifungal active against *Absidia* spp., *Aspergillus* spp., *Basidiobolus* spp., *Blastomyces dermatitidis*, *Candida* spp., *Coccidioides immitis*, *Conidiobolus* spp., *Cryptococcus neoformans*, *Histoplasma capsulatum*, mucoraceous fungi, *Paracoccidioides brasiliensis*, *Rhizopus* spp., and

Rhodotorula spp. (Fig. 1). However, some fungi are intrinsically resistant to it including, *Alternaria* spp., *Aspergillus flavus*, *Aspergillus lentulus*, *Aspergillus terreus*, *Candida guilliermondii*, *Candida lipolytica*, *Candida lusitanae*, *Fusarium* spp.; some isolates of *Penicillium marneffe*, *Scedosporium* spp., *Sporothrix schenckii*, and *Trichosporon* spp. Secondary resistance is rarely seen and is induced by mutations in *ERG2*, *ERG3* and *ERG6* genes encoding ergosterol biosynthetic enzymes, thereby depleting fungal cell membrane ergosterol content.

Use in Pediatrics

Amphotericin B is approved for invasive fungal infections like candidiasis and cryptococcal meningitis in neonates and children. The pharmacokinetics of amphotericin B in children are largely similar to that observed in adults, though significant interindividual variability is noted. Mean clearance rates can vary from 0.12 to 0.039 L/hour/kg and the volume of distribution from 0.37 to 4.1 L/kg. It can attain up to 40–90% of plasma levels in the neonatal cerebrospinal fluid (CSF) by virtue of the immature blood-brain barrier. Based on these observation, amphotericin B deoxycholate is recommended in children at a dose of 0.7–1.0 mg/kg/day administered over 2–4 hour, with careful monitoring for toxicity and renal function (Table 1). Infusion-related toxicity is rare in neonates and younger children; as is nephrotoxicity (0–44%) as compared to adults (~53%). Hypokalemia has been observed in some neonates. Neonates clear amphotericin B most rapidly thus protecting them from nephrotoxicity which is further reduced by sodium loading. Neonates are recommended a dose of 1 mg/kg/day, while preterm neonates are administered 0.5 mg/kg/day.

Amphotericin B lipid formulations of amphotericin B are currently approved for pediatric treatment of refractory invasive aspergillosis, invasive candidiasis and mucormycosis. These formulations also show no significant difference in pediatric pharmacokinetics as compared to adults. All trials indicate body weight as the only cofactor influencing volume of distribution and clearance. Lipid formulations cause substantially less nephrotoxicity and infusion-related toxicity in children, especially with LAMB. Recommended doses for children are 3–4 mg/kg/day ABCD, 5 mg/kg/day ABLC and 3 mg/kg/day LAMB. Very few studies have evaluated lipid formulations in neonates. Neonatal invasive candidiasis is treated with 5 mg/kg/day ABLC or 3 mg/kg/day LAMB (Table 1). Lipid formulations do not reach the CSF in neonates.

AZOLES

Pharmacology, Spectrum and Resistance

Azole antifungals inhibit cytochrome P450-dependent, lanosterol 14- α -demethylase (CYP51), critical for ergosterol synthesis. This compromises cell membrane permeability, impairs membrane-associated oxidative enzymes, and leads to intracellular phospholipid accumulation and cell death. Azoles act considerably slower than polyene antifungals and their effect becomes evident only over several generations of fungal multiplication.

Azoles are broadspectrum agents. Fluconazole is active against *Blastomyces dermatitidis*, most *Candida* spp., *Coccidioides immitis*, *Cryptococcus neoformans*, *Histoplasma capsulatum*, *Rhodotorula* spp., and *Saccharomyces* spp. Itraconazole has a wider spectrum of activity than most azoles. It is active against *Aspergillus* spp., *Blastomyces dermatitidis*, *Candida* spp., *Coccidioides immitis*, *Cryptococcus neoformans*, *Epidermophyton* spp., *Histoplasma capsulatum*, *Malassezia furfur*, *Microsporium* spp., *Paracoccidioides brasiliensis*, *Sporothrix schenckii*, *Trichophyton* spp., and several dematiaceous fungi. Posaconazole is active against *Aspergillus* spp., *Blastomyces dermatitidis*, *Candida* spp., *Coccidioides immitis*, *Fonsecaea pedrosoi*, some *Fusarium* spp.,



Figure 1 Antifungal spectrum of agents recommended for children. Darker blocks denote moderate to excellent in vitro activity against corresponding pathogen; lighter blocks denote minimal activity and/or occasional resistance; and empty spaces denote no antifungal action.

Abbreviations: AMB, amphotericin B; FLUC, fluconazole; ITRA, itraconazole; VORI, voriconazole; POSA, posaconazole; ANID, anidulafungin; CASP, caspofungin; MICA, micafungin.

Table 1 Therapeutic doses of antifungal agents recommended for pediatric use

Antifungal	Neonates (0–30 days)	Infants (1 month–2 years)	Children (2–17 years)	Therapeutic drug monitoring
Amphotericin B deoxycholate	0.7–1 mg/kg/day	0.7–1 mg/kg/day	0.7–1 mg/kg/day	Not required
ABL	2.5–5 mg/kg/day	NA	5 mg/kg/day	Not required
ABCD	NA	3–4 mg/kg/day	3–4 mg/kg/day	Not required
LAMB	3–5 mg/kg/day	3–5 mg/kg/day	3–5 mg/kg/day	Not required
Fluconazole	25 mg/kg loading dose; 12 mg/kg/day maintenance dose	12 mg/kg/day	6–12 mg/kg/day	Not clear, as recent Australian data show variable drug level in adults
Itraconazole	NA	NA	2.5–5 mg/kg 12 hourly	Trough > 0.5 mg/L
Posaconazole	NA	NA	200–400 mg 6–12 hourly	Trough > 1 mg/L
Voriconazole	4–6 mg/kg 12 hourly loading dose; 2–3 mg/kg 12 hourly maintenance dose	4–6 mg/kg 12 hourly loading dose; 2–3 mg/kg 12 hourly maintenance dose	7–9 mg/kg IV 12 hourly; 200–400 mg oral 12 hourly	Trough 1.0–5.5 mg/L
Anidulafungin	1.5 mg/kg/day	1.5–3.0 mg/kg/day	1.5–3.0 mg/kg loading dose; 0.75–1.5 mg/kg/day maintenance dose	Not required
Caspofungin	25 mg/m ² /day	50 mg/m ² /day	70 mg/m ² /day loading dose; 50 mg/m ² /day maintenance dose	Not required
Micafungin	10 mg/kg/day	2–4 mg/kg/day	2–4 mg/kg/day	Not required

Abbreviations: ABL, amphotericin B lipid complex; ABCD, amphotericin B colloidal dispersion; LAMB, liposomal amphotericin B.

Histoplasma capsulatum, the dermatophytes and mucoraceous fungi. Voriconazole is effective against *Alternaria* spp., *Aspergillus* spp., *Bipolaris* spp., *Blastomyces dermatitidis*, all *Candida* spp., including fluconazole resistant *C. krusei* and *C. glabrata*, *Coccidioides immitis*, *Cryptococcus neoformans*, *Histoplasma capsulatum*, *Fusarium* spp., *Paracoccidioides brasiliensis*, *Paecilomyces* spp., *Penicillium marneffei*, *Pseudallescheria boydii*, *Saccharomyces cerevisiae*, *Scedosporium* spp., and *Trichosporon beigelii* (Fig. 1).

Despite their broadspectrum activity, some fungi are intrinsically resistant to azoles. *Candida krusei* is intrinsically resistant to fluconazole and itraconazole. Certain *Aspergillus* spp., *Fusarium* spp., *Scedosporium* spp., *Pseudallescheria boydii* and the mucoraceous fungi are intrinsically resistant to fluconazole, itraconazole and voriconazole. *Sporothrix schenckii* is intrinsically resistant to voriconazole and *Trichosporon* spp. to fluconazole. Secondary resistance results from point mutations, gene amplification, and over-induction of the *ERG11* gene encoding synthesis of 14- α -lanosterol demethylase. Over expression of energy-dependent efflux pumps including, the ATP-binding cassette (ABC) super-family proteins and the major facilitator super-family (MFS) proteins, also play a major role in preventing intracellular accumulation and action of azoles.

Azoles either inhibit or are metabolized by cytochrome P450 isoenzymes CYP3A4, CYP2C9 and CYP2C19. Thus any drug which inhibits, induces or utilizes these isoenzymes shows wide interactions with azoles. Itraconazole and voriconazole are particularly notorious. Drugs such as astemizole, cisapride, halofantrine, pimozone, quinidine, terfenadine, ergot alkaloids are contraindicated with azoles because they precipitate toxicity. On the other hand, rifabutin, phenytoin, omeprazole, benzodiazepines and non-nucleoside reverse transcriptase inhibitors (NNRTIs) need to be monitored along with azoles for therapeutic failure. It is also highly desirable that itraconazole, voriconazole and posaconazole should be placed on therapeutic drug monitoring.

Fluconazole

Fluconazole is approved for oropharyngeal, esophageal, and invasive candidiasis in children. Its plasma clearance is significantly more rapid in children yielding a significantly shorter half-life than adults. Drug clearance may be reduced in premature infants during the first few days of life. Population-based pharmacokinetics recommends a dose of 6–12 mg/kg/day in children over 4 weeks of age (Table 1). Severe infections such as invasive candidiasis require a minimum dose of 12 mg/kg/day to achieve an area under the concentration curve (AUC)/minimum inhibitory concentration (MIC) index more than 50. Dose adjustment is recommended in children with serum creatinine more than 1.3 mg/dL, which does not resolve within 96 hour. Fluconazole prophylaxis for early prevention of candidiasis is administered at 3–6 mg/kg twice weekly during first 42 days of life in 23–29 week infants and at 6 mg/kg doses every 72 hour or 3 mg/kg/day for late prevention. Most common side effects in children include gastrointestinal disturbances (8%), elevated hepatic transaminases (5%) and skin reactions (1%). The Infectious Diseases Society of America (IDSA) recommends a loading dose of 25 mg/kg followed by maintenance dose of 12 mg/kg/day in infants and neonates, to rapidly achieve therapeutic levels and an AUC of more than 400 mg hour/L (Table 1).

Itraconazole

Although itraconazole is not approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for use in individuals less than 18 years of age, but this has been employed in children for salvage and compassionate therapy. Itraconazole oral solution is given for oropharyngeal

candidiasis at 2.5 mg/kg twice daily (cumulative 3–5 mg/kg/day, up to a maximum of 100 mg) in children more than 5 years of age (Table 1). Itraconazole oral solution is not available in India. The pharmacokinetics of oral tablet is complex, because their gastrointestinal absorption varies with acid content and food intake. Therefore, therapeutic drug monitoring becomes essential while the patient is on itraconazole oral tablets. Cystic fibrosis and allogeneic bone marrow transplant children with invasive fungal infection are prescribed 5 mg/kg twice daily (maximum 200 mg) oral itraconazole with therapeutic drug monitoring and a target trough level of 0.5 μ g/mL. Limited studies of intravenous itraconazole use in children aged 7 months to 17 years indicate a dosing approach based on body weight. The British National Formulary for Children recommends 2.5 mg/kg every 12 hour (maximum 200 mg) for 2 days followed by 2.5 mg/kg once daily for a maximum of 12 days. Common side effects in children include vomiting (12%), abnormal liver function tests (5%), and abdominal pain (3%). Nephrotoxicity becomes an important issue due to the cyclodextrin present in itraconazole intravenous solution. Pharmacokinetics data for neonates are not available.

Posaconazole

Posaconazole is a new generation broadspectrum azole, particularly, important for its activity against mucoraceous fungi. It has not yet been approved for patients less than 18 years of age. Few studies have examined its pharmacokinetics in children receiving salvage therapy at 800 mg/day (Table 1). Though no significant side effects different from adults have been noted, systematic trials are currently underway to elucidate its dosage, safety and efficacy in children more than 4 weeks old.

Voriconazole

Voriconazole is a third-generation, broadspectrum azole. It is approved for treatment of invasive fungal infections in children 2 years or older. Unlike its nonlinear pharmacokinetics in adults, voriconazole exhibits linear pharmacokinetics in children, thereby requiring higher dose in children to attain comparable therapeutic levels as in adults. Children also have lower oral bioavailability than adults (45–65% vs 96%) probably due to greater first-pass metabolism.

For children, 12 years or older intravenous voriconazole is prescribed at 6 mg/kg twice daily on day 1 followed by 4 mg/kg twice daily. Oral voriconazole is administered for the first 24 hour, with a 12 hourly loading dose adjusted by body weight. Children weighing more than 40 kg are given 400 mg, while those weighing less than 40 kg receive 200 mg. Subsequent oral maintenance dose for those weighing more than 40 kg is 200 mg twice daily, raised to 300 mg twice daily in case of inadequate response. Children weighing less than 40 kg receive 100 mg twice daily increased to 150 mg twice daily in case of inadequate response. Children aged 2–11 years eliminate voriconazole significantly faster than adults. This is mediated by faster CYP2C19 cytochrome metabolism and flavin-containing monooxygenase-3 activity. Hence, children aged 2–11 years are recommended 200 mg twice daily oral and 7–9 mg/kg twice daily intravenous voriconazole, with no loading dose over first 24 hour. If the child is unable to tolerate high dose therapy, the dose should be brought down to 4 mg/kg twice daily (Table 1). Intravenous voriconazole should be infused at a maximum rate of 3 mg/kg/hour over 1–2 hour. Pharmacokinetic data is sparse for neonates and children less than 2 years of age. The FDA has not allowed any study in children less than 24 months given the deleterious effects of voriconazole on the developing retina. Limited studies recommend a 4–6 mg/kg 12 hourly loading dose followed by 2–3 mg/kg 12 hourly in neonates and preterm infants, although doses as high as 9 mg/kg 12 hourly have also been

administered to maintain adequate trough levels. Therapeutic drug monitoring is recommended.

Common adverse effects in children include elevated hepatic transaminases, vision abnormalities, skin rash and photosensitivity. Its use in small children involves the concern of long-term adverse effects on the developing retina. Long-term administration in immunosuppressed patients is possibly linked to aggressive squamous cell carcinoma and should be guarded against during prolonged therapy in children.

ECHINOCANDINS

Pharmacology, Spectrum and Resistance

Echinocandins are semi-synthetic glycopeptides that inhibit the production of 1,3- β -glucan, a critical fibrillar fungal cell wall component. This compromises fungal cell wall integrity thereby disrupting its shape, ion and small molecule exchange, surface presentation of molecules and the cell's internal milieu. Echinocandin action is rapid, noncompetitive and most prominent at growing hyphal tips and budding sites. It eventually kills the fungal cell by osmotic lysis. Echinocandins are fungicidal toward most yeasts and fungistatic towards filamentous fungi.

Echinocandins are active against most *Aspergillus* spp., *Candida* spp. including those resistant to azoles and *Saccharomyces cerevisiae*. However, *Candida parapsilosis*, *Candida guilliermondii*, and *Candida famata* require higher minimum inhibitory concentrations than other *Candida* spp. Echinocandins are also effective against mycelial (and not yeast) forms of *Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Coccidioides immitis* (Fig. 1). They show variable efficacy against dematiaceous fungi and *Pneumocystis jirovecii* and only minimal activity against *Fusarium* spp., *Pseudallescheria boydii*. Echinocandins are particularly effective against amphotericin B and fluconazole resistant *Candida* and *Aspergillus* isolates. Echinocandins target glucan synthase encoded by the *FKS1*, *FKS2* and *RHO1* genes, essential for 1,3- β -glucan synthesis. *Cryptococcus neoformans*, *Fusarium* spp., *Scedosporium* spp., *Trichosporon asahii* and the mucoraceous fungi are intrinsically resistant to echinocandins, because they do not synthesize 1,3- β -glucan for their cell wall. Secondary resistance is conferred by *FKS1* and *FKS2* point mutations and substitutions which alter glucan synthase activity.

Anidulafungin

Anidulafungin demonstrates linear pharmacokinetics and longest half-life among echinocandins. Advanced safety and efficacy trials in children aged 2–11 years and 12–17 years reveal pharmacokinetics similar to adults with no serious adverse effects. These studies recommend a weight-adjusted regime with 1.5–3.0 mg/kg loading dose followed by 0.75–1.5 mg/kg/day maintenance dose for children aged 2–17 years (Table 1). A 1.5 mg/kg/day dose produces comparable therapeutic levels in infants and neonates. Despite these studies, anidulafungin has not been approved for use in children by the FDA and EMEA, given the lack of sufficient clinical experience.

Caspofungin

Caspofungin is licensed by the EMEA and FDA (2008) for use in children and neonates suffering from invasive aspergillosis, invasive candidiasis and for empiric therapy in febrile neutropenic patients. Studies in children aged 2–17 years showed that a weight-adjusted dose of 1 mg/kg/day offered suboptimal exposure. Body surface-area adjusted dosing at 50 mg/m²/day yielded therapeutic levels comparable to adults. Further population pharmacokinetic studies confirmed these findings and also recommended a dose of 25 mg/m²/day for neonates and infants up to 3 months of age

(Table 1). Combined analysis of five pediatric trials show good tolerance in children. Common adverse effects including fever (11.7%), elevated transaminases (6.5%), skin rash (4.7%) and therapeutic success rates are similar to adults.

Micafungin

Micafungin is approved by the EMEA (2008) and FDA (2013) for treatment and prophylaxis of invasive candidiasis in pediatric patients with febrile neutropenia and allogeneic stem cell transplant. It is administered at 100 mg/day or 2 mg/kg/day, if the child weighs less than 40 kg. The dose may be raised to 200 mg/day or 4 mg/kg/day in cases of invasive candidiasis. Esophageal candidiasis is treated with 150 mg/day (3 mg/kg/day for ≤ 40 kg), and prophylaxis is administered at 50 mg/day (1 mg/kg/day for ≤ 40 kg) (Table 1). Multicenter trials in children aged 2–17 years indicate no dose-limiting toxicities, linear pharmacokinetics similar to adults, and no variations in drug clearance, distribution volume and drug half-life on repeated dosing. Combined analysis of six pediatric trials revealed adverse events in 26.7% children, but no different from adults. Micafungin clearance is significantly faster in neonates and premature infants than that predicted by body weight alone. Trial data and pharmacokinetic modeling suggest higher doses for extremely low birth weight neonates (15 mg/kg/day), low birth weight neonates (7 mg/kg/day) and normal neonates (4 mg/kg/day). A higher 10 mg/kg/day dose is recommended for neonatal central nervous system fungal infections. The appropriate dose of micafungin for neonates is still under debate. Based on animal studies showing liver tumorigenesis, the EMEA advises careful monitoring of liver function and early discontinuation of micafungin with increasing hepatic transaminases.

FLUORINATED PYRIMIDINES

Pharmacology, Spectrum and Resistance

Flucytosine is a low molecular weight, water-soluble, fluorinated pyrimidine analog which inhibits fungal RNA and DNA synthesis. It is internalized by fungus-specific cytosine permease and activated by fungal cytosine deaminase to the antimetabolite, 5-fluorouracil (5-FC). 5-FC competitively replaces uracil in fungal RNA, causing RNA miscoding and disrupting protein synthesis. It also inhibits *thymidylate synthase* thereby inhibiting fungal DNA synthesis.

Flucytosine is active against most *Candida* spp., *Cryptococcus neoformans*, *Cladosporium* spp., *Fonsecaea* spp., *Phialophora* spp., and *Saccharomyces* spp. Intrinsic resistance is seen in some strains of *Candida albicans*, *Candida krusei*, *Cryptococcus neoformans* and *Aspergillus* spp., and is conferred by mutations altering cytosine deaminase activity. Most zygomycetes and dermatophytes are intrinsically resistant to flucytosine. Secondary resistance is frequently acquired during treatment, especially when flucytosine is used for monotherapy. Point mutations in the *FCY1* and *FCY2* genes encoding for purine-cytosine permease and cytosine deaminase, respectively, are commonly responsible for secondary resistance.

Use in Pediatrics

Although systematic flucytosine pharmacokinetic data for children is unavailable, limited studies indicate high interindividual variability in clearance rates and distribution volumes in neonates. Currently, recommended doses in children are similar to that in adults at 100 mg/kg/day in 3–4 divided doses. Accumulation of flucytosine due to immature pediatric renal function can lead to marrow toxicity and therapeutic drug monitoring is advised to maintain plasma levels between 40–60 μ g/mL. Flucytosine is recommended in combination with amphotericin B especially for cryptococcal meningitis.

IN A NUTSHELL

1. Each antifungal has its pharmacokinetic peculiarities in children and cannot be prescribed simply at weight-adjusted doses.
2. Despite their immature renal function, small children and neonates clear antifungals much more rapidly than adults.
3. Amphotericin B deoxycholate induced infusion-toxicity and nephrotoxicity are less in neonates and small children.
4. Fluconazole is rapidly cleared by infants and neonates requiring a higher loading dose.
5. Itraconazole is prescribed at weight-adjusted doses, but therapeutic monitoring is recommended, given its unpredictable absorption.
6. Voriconazole demonstrates linear pharmacokinetics, higher first-pass metabolism and lower bioavailability in children thus requiring higher doses. Voriconazole may be avoided in neonates due to possible toxicity during retinal development.
7. Therapeutic drug monitoring is recommended for itraconazole, posaconazole, voriconazole and may also be monitored for fluconazole.
8. Caspofungin is administered at doses adjusted for body surface-area, since weight-adjusted doses pose a high risk of therapeutic failure.
9. Despite its linear pharmacokinetics, micafungin is cleared much faster by neonates and infants. Clearance cannot be predicted by body weight alone and higher doses are recommended.
10. It is recommended to prescribe flucytosine in combination with amphotericin B to prevent drug resistance.

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Chapter 33.3

Candidiasis

Kheya Ghosh Uttam

Candidiasis is the most common fungal disease found in humans. *Candida* is also the fourth most common organism recovered from blood cultures in hospitalized patients. In India, there are only few diagnostic mycotic laboratories and centers which carry routine medical autopsies. Thus, there is limited data regarding exact frequency of mycotic infections. However, India being a tropical country getting heavy rainfall, having few millions HIV-infected population, less than optimal infection control practices and rampant use of systemic steroids, certainly has a high prevalence of opportunistic mycoses. Recent data suggest that invasive candidiasis is the most common invasive mycotic infection across India. Incidence varies from 1–12 per 1,000 admissions in different hospitals across the country. Neonatal ICUs, pediatric ICUs and surgical ICUs report high incidence of candidemia. Candidiasis may be superficial or systemic (invasive) and with wide clinical presentations.

EPIDEMIOLOGY

Candida is a small (4–6 µm) oval-shaped yeast. *Candida* species are the component of normal flora of human beings and reproduce by budding. Alteration of balance between the host resistance and the normal microbial flora predispose to candidiasis.

Agent Of 163 species of the genus *Candida*, 20 are considered significant. The most common pathogenic species is *Candida albicans*. Over the past two decades, there is significant increase of non-*albicans* *Candida* species including *Candida tropicalis*, *Candida krusei*, *Candida glabrata* and *Candida parapsilosis*. In India, non-*albicans* *Candida* species are identified in 30–90% cases of invasive candidiasis. *C. tropicalis* is the most common species among non-*albicans*. Resistance to fluconazole is seen in less than 10% strains of *C. tropicalis*.

Risk factors Most studies in India identify prolonged hospitalization, central venous access, total parenteral nutrition, use of broadspectrum antibiotics for long duration, mechanical ventilation, major abdominal surgery and immunosuppression (corticosteroid or other immunosuppressive therapy, neutropenic patients, children with endocrine disorders, HIV, burn and malignancy and neonates) as risk factors for candidemia.

PATHOGENESIS

Candida species has several properties responsible for its pathogenicity in immunocompromised states. These include adherence to epithelial and endothelial cells, proteinase production, pseudohyphae formation, phenotypic switching, phospholipase production and antigenic modulation due to pseudohyphae formation.

Candida normally inhabits the gastrointestinal tract, the female genital tract and the skin. The portal of entry is usually mucosal or skin. Intact epithelial barriers, normal neutrophils, lymphocyte and macrophage function, adequate antibody and complement level, and normal bacterial flora are the host factors which prevent invasion. During penetration of skin or mucous membrane, the yeast cells of *Candida* are transformed into hyphal form. Hyphae being larger than the yeast are more resistant to phagocytosis. It is believed that high concentration of phospholipase enzyme at the tip of the hyphae may be related to the greater invasiveness of

this form. The phagocytic cells, neutrophils and monocytes, are the most important defensive guard against this invasion. They develop candidacidal activity following fungal penetration, which involve myeloperoxidase and superoxide or cationic proteins. The phagocytic cell activity is crucial for protection against invasive candidiasis. Thus, increased incidence of invasive candidiasis is seen in neutropenic patients. *C. glabrata* can cause invasive candidiasis even though it does not transform into pseudohyphal or hyphal form.

CLINICAL FEATURES

Candidiasis can affect different organ systems and the spectrum varies from benign superficial infections to deep invasive or systemic infections.

Superficial Candidiasis

Oral thrush Oral thrush is common in normal infants in the first week of life. Thrush in older children is unusual unless they have recently received antimicrobials or are immunosuppressed. In older children, corticosteroid inhalation for treatment of bronchial asthma is the most common predisposing factor. Typically, the lesions are few or extensive, adherent creamy white, discrete or confluent plaques on the buccal, gingival, palatal or lingual mucosa. Oral thrush may be asymptomatic or it may cause pain and decreased feeding (**Figs 1 and 2**).

Angular cheilitis Angular cheilitis is caused by *Candida* at the corners of the mouth, often in association with a vitamin B₁₂ or iron deficiency. The patient presents with sore, erythematous fissured lesions affecting the angles of the mouth and may be associated with denture stomatitis. A significant number of patients with HIV have angular cheilitis (**Fig. 3**).

Diaper dermatitis Maceration and wet diapers predispose infants to diaper dermatitis. An erythematous maculopapular rash in the perineum, inguinal fold and intertriginous areas is commonly seen initially. The lesions coalesce and become confluent with satellite pustules. Pustules, vesicles and scales may be seen. Moist areas, such as axilla or neck folds may also be involved. The precipitating factors for *Candida* infection include are mechanical friction, prolonged contact with urine and feces, application of topical ointment and alteration of skin pH.

Congenital cutaneous candidiasis These lesions may be seen in babies born to a mother with *Candida* amnionitis or after prolonged rupture of membranes in an infected mother. A red



Figure 1 Oral thrush in a neonate



Figure 2 Oral thrush in older child



Figure 3 Angular cheilitis

maculopapular or pustular rash or erythema is characteristically present at birth.

Vaginal infection Vulvovaginitis due to candida occurs in young girls, middle aged and pregnant women, diabetic patients, and in those on prolonged antibiotic or oral contraceptive therapy. Patients present with thick, odorless, curdy or cheesy discharge with intense pruritus or burning sensation and dyspareunia. The vagina and labia may be erythematous and edematous.

Balanitis and balanoposthitis Balanitis and balanoposthitis are found primarily in uncircumcised adolescent boys. The lesions are whitish, pustular associated with erythema and pruritus, and found over glans. Sometimes edema and erosion of prepuce leads to acquired phimosis. As similar lesions may be produced by other conditions, laboratory support should be sought for the diagnosis of genital candidiasis.

Paronychia and onychomycosis Paronychia is an inflammation of the nail fold primarily affecting the finger nails and may

involve the toe nails. These conditions may occur in immunocompetent children but are more commonly associated with immunosuppression, diabetes mellitus, hypoparathyroidism, or adrenal insufficiency (*Candida* endocrinopathy syndrome). Paronychia and onychomycosis is usually caused by *Trichophyton* and *epidermophyton* but can also be due to *Candida* species, which usually involves the fingernails.

Intertrigo Intertrigo is an erythematous inflammation of the skin folds. These red pustular lesions often develop superimposed bacterial infections. When secondarily infected, may develop lymphangitis and lymphadenopathy. It occurs predominantly in adolescent females.

Chronic mucocutaneous candidiasis Chronic mucocutaneous candidiasis refers to infection at multiple sites in skin, mucous membrane, nails and hair which persists despite antifungal therapy. The disease usually starts in infancy or within the first two decades of life. The lesions are hyperplastic and nodular. These may be mild and limited to an area or may be severe characterized by exophytic growths on skin. Despite severe cutaneous involvement, they rarely develop invasive candidiasis. Underlying pathology includes defective cell mediated immunity where the T lymphocytes fail to proliferate or to stimulate cytokines in response to *Candida* antigen. Invasive candidiasis is rare because the function of neutrophil remains intact. Chronic mucocutaneous candidiasis is associated with many underlying conditions including endocrinopathies, HIV infection, DiGeorge syndrome and hyper IgE syndrome. Almost half of the patients of this group has autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) syndrome. The lesions are followed by onset of hypoparathyroidism, adrenal insufficiency, autoimmune thyroiditis, Grave's disease, chronic active hepatitis, alopecia, pernicious anemia, primary hypogonadism, dental enamel dysplasia, vitiligo, and pitted nail dystrophy.

Keratoconjunctivitis Candidal keratoconjunctivitis presents with conjunctival edema, cheesy discharge and progressive corneal ulceration. This occurs following long-term use of topical corticosteroids.

Deep invasive candidiasis Deep invasive candidiasis usually results from hematogenous spread. But it may result from contiguous spread from skin as in superficial erosions, deep wounds, catheter related or from alimentary tract to other abdominal organs during perforation of GI tract.

Gastrointestinal candidiasis Candidiasis may involve esophagus and rarely stomach, in immunosuppressed children. Esophagitis may be asymptomatic or it may cause burning sensation in throat and suprasternal area of chest, dysphagia, and anorexia. Upper GI endoscopy reveals white plaques on the mucosal surface, notably in the distal third of esophagus. Nausea and vomiting are common in young children. Many may not have associated oral thrush. Stomach or intestinal ulcers may occur. Atrophic glossitis, chronic hyperplastic candidiasis may occur in critically ill children. A syndrome of mild diarrhea occurs in normal individuals. *Candida* is not considered as a true enteric pathogen, its presence mostly in stool likely reflects recent antimicrobial therapy. Retrograde migration from GI tract into biliary tract may cause gallbladder infection.

Pulmonary infection *Candida* is commonly isolated from respiratory secretions as it frequently colonizes the respiratory tract. Mere isolation of *Candida* species from respiratory tract does not imply invasive pulmonary infection. Demonstration of tissue invasion is essential to diagnose *Candida* pneumonia or tracheitis. It is a rare condition seen in immunosuppressed children and in those intubated for long periods, and on broadspectrum antibiotics. The pulmonary infection may cause fever, cough, abscesses, reticulonodular infiltrates, and effusion.

Urinary tract infection Candiduria may reflect colonization or may be the only manifestation of urinary tract disease. Most of the patients are asymptomatic. More often, candiduria is associated with instrumentation, *in situ* catheter, abnormality of the urinary tract or immunosuppressed host especially in diabetics. Rarely, masses of *Candida* (fungal balls) may obstruct ureters and cause obstructive nephropathy. *Candida* casts in the urine suggest renal tissue infection.

Other infections Any organ in human body can be infected by *Candida*. Once *Candida* enters intravascular compartment, dissemination may occur in any of the deep organs especially in immunocompromised patients and neonates. Endocarditis, myocarditis, meningitis, and chorioretinitis are common while liver, spleen bone and joints are less commonly involved. Hepatosplenomegaly may occur in immunosuppressed, severely neutropenic patients with chronic fever, variable abdominal pain, and abnormal liver function tests. It may occur with or without fungemia. *Candida* endophthalmitis is characterized by one or more focal white lesions in the retina associated with haziness of the overlying vitreous. Presence of chorioretinitis indicates high probability of formation of abscess in deep multiple organs. Thus, an ocular examination is a must in all children with candidemia. Rarely endocrine glands, pancreas and skeletal muscles may get involved. If there is persistent candidemia, then the occult organ involvement should be considered.

Disseminated candidiasis This occurs in neonates, especially in premature infants, in an intensive care setting, and should be suspected when the baby fails to respond to adequate dose of antibiotics. These infants have unexplained feeding intolerance, cardiovascular instability, apnea, new or worsening respiratory problems, fluctuating glucose levels, thrombocytopenia, or hyperbilirubinemia. Disseminated candidiasis is also common in children with hematological malignancies, and in those undergoing bone marrow or organ transplantation. Treatment for presumptive infection is often undertaken because candidemia is not identified in many such patients.

LABORATORY DIAGNOSIS

The greatest challenge to diagnose *Candida* infection is to differentiate an isolate as mere colonization or as infection. The other diagnostic difficulty is absence of a sensitive serological test.

Direct Examination

Skin or nail scrapings, sputum, swab from patches in the mouth, throat or vagina are examined in KOH, wet mount preparation for visualization of yeast cells, pseudohyphae or hyphae. Gram staining is performed to see all these forms of the fungus. Absence of organisms on hematoxylin-eosin stained specimen does not exclude the diagnosis. Calcofluor white stain may be used to highlight the fungal elements. Demonstration of pseudohyphae is highly significant as it indicates tissue invasion.

Fungal Culture

Isolation of *Candida* species in blood culture is the most important diagnostic tool for fungal infection. The yield of old blood culture technique was very low. The clinical specimens are cultured with antibacterial antibiotics and incubated at 25°C and 37°C. Different species can be identified by their colony characteristics (**Figs 4A and B**), biochemical tests such as sugar fermentation and assimilation reactions.

Serological Tests

Despite extensive efforts, there is no current antigen or antibody detection test available which has good sensitivity and specificity. A positive antibody detection test does not necessarily indicate infection as it is unable to differentiate antibodies formed by colonization or by deep infection. Negative antibody test also does not rule out infection as immunocompromised patients may not be able to mount adequate antibody response. Antigen detection is likely to emerge as an important method of serodiagnosis in coming years. Detection of cell wall component such as cell wall mannoprotein (CWMP) β -(1,3)-D- glucan are undergoing several studies to establish their utility.

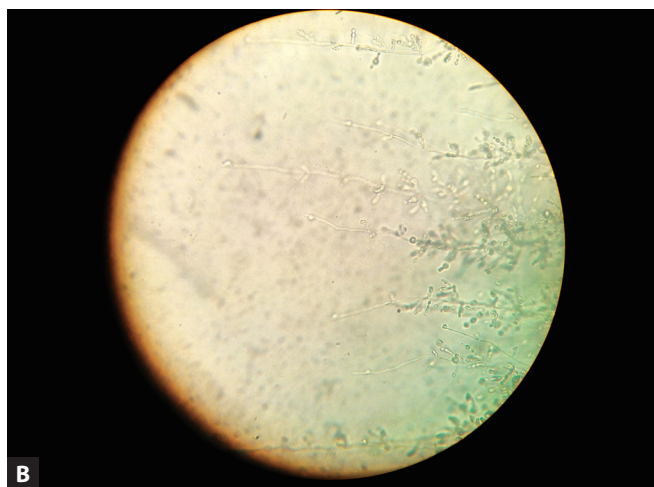
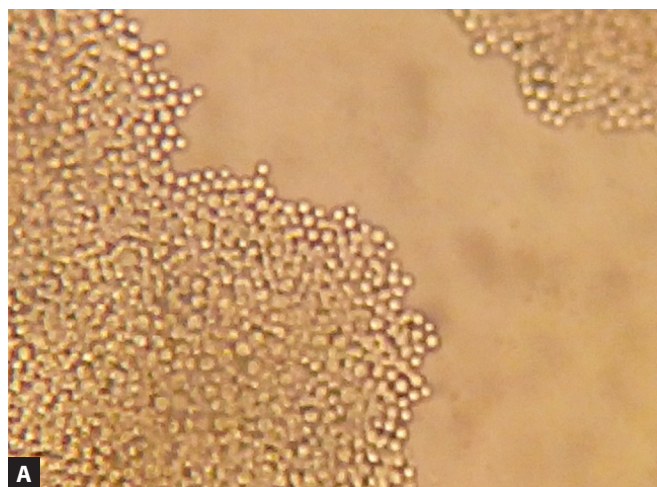
TREATMENT

Superficial Candidiasis

Topical nystatin is used for oral and mucocutaneous candidiasis. Topical azoles are used and are preferable mode of treatment. Vulvovaginal candidiasis is treated with azole or nystatin suppository and may require oral fluconazole.

Invasive Candidiasis

As there is no reliable way to distinguish between benign candidemia or colonization and deep invasive candidiasis, all children with candidemia should be treated with antifungal drugs. In addition, the



Figures 4A and B (A) *Candida albicans* in corn meal agar; (B) *Candida glabrata* in corn meal agar

indwelling catheter, infected valve or prosthesis should be removed. Selection of the initial antifungal depends upon previous use of azole either as prophylaxis or therapy, severity of the disease, organ involvement, immune status of the patient, common isolates of that unit and their sensitivity pattern. Once the species is identified and antifungal susceptibility report is available the treatment is altered accordingly. Presently, majority of *C. albicans* are sensitive to fluconazole. *C. glabrata* and *C. krusei* are less sensitive to fluconazole and more sensitive to polyenes and echinocandins.

The drugs used for the treatment of candidiasis with their doses are shown in **Table 1**. Polyenes (amphotericin B and its lipid preparation), azoles and echinocandins are available treatment options. No agent has been clearly identified superior to other. However, amphotericin B or echinocandins are preferably used as first line drug in severely ill or unstable patients with candidemia in certain centers.

In patients with meningitis, the recommended treatment is intravenous polyenes plus flucytosine. Renal function should be monitored closely in patients who receive amphotericin B. Removal of infected prosthetic valve and prolonged antifungal therapy is required for *Candida* endocarditis. *Candida* endophthalmitis often require partial vitrectomy in addition to treatment with IV polyenes and flucytosine. Candiduria in a hospitalized patient with or without a catheter may represent colonization. However, systemic antifungal treatment with fluconazole should be started in seriously ill patients, in immunocompromised, in patients with obstructive renal diseases and in preterm low birth weight babies. Antifungal therapy should be continued for 2 weeks after the last positive blood culture.

Table 1 Recommended antifungals for treatment of invasive candidiasis in children

Drugs	Dose and route	Comment
Amphotericin B deoxycholate	1–1.5 mg/kg/day, IV	Broadspectrum, nephrotoxic
Liposomal amphotericin B	3–5 mg/kg/day, IV	Broadspectrum
Fluconazole	6–12 mg/kg/day, IV and oral	Most commonly used
Voriconazole	6–8 mg/kg/day, IV and oral	Multiple drug interaction
Caspofungin	50 mg/m ² /day, IV	Broad spectrum

PROPHYLAXIS

Prophylaxis treatment with antifungal agent is controversial. It should not be encouraged as there will be increased resistance to common antifungals. Increase incidence of *non-albicans candida* species is also a concern following prophylactic use of antifungal drugs. Prophylactic fluconazole is recommended for patients undergoing bone marrow or organ transplant. Till now, there is no consensus for use of antifungal prophylaxis in neutropenic patients.

IN A NUTSHELL

1. Candidiasis is the most common fungal disease found in human.
2. In India, incidence of invasive candidiasis varies from 1–12/1,000 hospital admission.
3. Though the most common pathogenic species is *Candida albicans*, there is significant increase of non-albicans *Candida* in the past two decades.
4. Presumptive antifungal treatment should be given to a child with risk factor who fails to improve after adequate dose of antibiotic.
5. Prophylaxis antifungal treatment should be strongly discouraged, except in bone marrow and organ transplant patients.

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Chapter 33.4

Aspergillosis

Kana Ram Jat

Aspergilli, the ubiquitous fungi, have about 185 species with *Aspergillus fumigatus* (AF), *Aspergillus niger*, and *Aspergillus flavus* being most common that cause diseases in human. Human are exposed to spore such as conidia of *Aspergillus*, which float in air, almost daily. Usually, inhaled airborne conidia are cleared by macrophage and neutrophil-mediated phagocytosis in normal people and rarely cause disease. Aspergilli cause disease in immunosuppressed person, in genetically susceptible person or after inhalation of very high doses of conidia.

Aspergillus may cause three separate groups of diseases: (1) Hypersensitivity (e.g., allergic bronchopulmonary aspergillosis (ABPA); *Aspergillus* mediated asthma and hypersensitivity pneumonia; and malt worker's disease), (2) saprophytic (non-invasive e.g., aspergilloma) and (3) invasive disease [e.g., invasive aspergillosis (IA)] depending on host's immune status and quantity and virulence of inhaled *Aspergillus*. Of these, ABPA is an important and common disease caused by *Aspergillus* species. *Aspergillus mediated asthma* refers to an exacerbation of known asthma following inhalation of *Aspergillus* spores. It is a Th2 hypersensitivity lung disease caused by sensitization to *Aspergillus* antigens that occur mainly in people with cystic fibrosis or asthma. *Hypersensitivity pneumonitis* is an extrinsic alveolar alveolitis caused by repetitive inhalation of *Aspergillus* conidia and manifest as cough, fever, and breathlessness. Eosinophilia is absent in blood and sputum.

ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

Epidemiology

Aspergillus fumigatus is responsible for majority of ABPA cases. Overall, these occur in about 1–2% of children with asthma and 2–15% of patients with cystic fibrosis (CF). One study from India showed unusually high prevalence of ABPA where 15% of children with perennial asthma and 6.5% of total asthmatic children screened were found to have ABPA. A recent study from Delhi revealed 18.2% prevalence of ABPA in children with CF. Though sensitization to *Aspergillus* is common in asthmatic and CF patients (20–25% of asthmatic patients and 31–59% of CF patients), only a small percentage of these patients develop ABPA. Low body mass index, low CF score, age more than 12, atopy, eosinophilia, colonization with other fungi are some of the risk factors for developing ABPA in CF patients.

Pathophysiology

Inhaled *A. fumigatus* spores germinate into hyphae within bronchi and release various proteins (e.g., proteases, superoxide dismutases, hemolysin, etc.) and toxins which induce production of inflammatory cytokines and chemokines, such as IL-6, IL-8 that leads to disruption of pulmonary epithelium and persistent abnormal immunological inflammatory response. People with asthma and CF that develop ABPA are found to have some genetic susceptibility factors. Lack of HLA-DQ2 and presence of HLA-DR2 and/or DR5 had increased risk of ABPA when exposed to *Aspergillus*, whereas presence of HLA-DQ2 (especially HLA-DQB1*0201) is supposed to have protective effect against ABPA. Polymorphism of IL-4 receptor α chain and 1082GG genotype of the IL-10 promoter may also have a role in pathogenesis of ABPA in cystic fibrosis.

Clinical Features

Allergic bronchopulmonary aspergillosis results in exacerbation of asthma or CF with lung infiltrates on chest X-ray along with sputum and blood eosinophilia. The ABPA presents with worsening cough and wheezing which may be accompanied by fever, malaise, and expectoration of brown plugs. The ABPA may be in chronic form with intermittent acute exacerbations. Chest examination may reveal findings of underlying disease, i.e., asthma or CF along with wheeze and/or crepitations. A child with associated bronchiectasis may have clubbing, weight loss, and coarse crepitations. The ABPA should be suspected in asthmatics that are difficult to control or inadequately treated with marked eosinophilia. Children with CF who show wheezing, pulmonary infiltrates and reduced lung function despite adequate treatment for CF should be investigated for ABPA. Clinical staging of ABPA (Patterson staging) is tabulated in **Box 1**.

Radiology Findings

Central bronchiectasis (**Fig. 1**) and fleeting shadows are the most common radiological findings in ABPA both in children and adults. The other findings are large homogeneous shadow (patchy, lobar or triangular) mostly in upper lobe without volume loss, *tram line appearance* (fine parallel lines from hila due to inflamed airways), toothpaste shadows, gloved-finger shadows due to mucus impaction, dilated and totally occluded bronchi, bronchial wall thickening, and ring shadows. High resolution computerized tomography (HRCT) is the investigation of choice to delineate lung lesions in ABPA.

Box 1 Clinical stages for allergic bronchopulmonary aspergillosis (ABPA)

Stage I:	Acute exacerbation of disease with most of the classical features
Stage II:	Remission
Stage III:	Recurrence of exacerbation with two times increase in IgE levels
Stage IV:	Where patients need continuous steroids to control the disease
Stage V:	Fibrotic stage which responds poorly to steroids and may lead to pulmonary hypertension and cor pulmonale

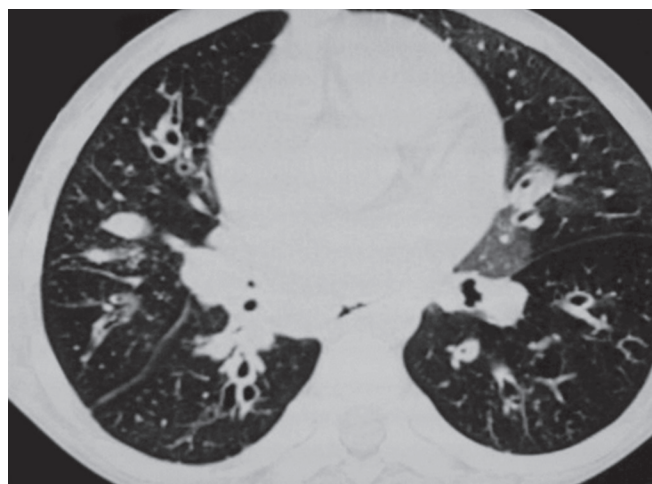


Figure 1 An asthmatic child with allergic bronchopulmonary aspergillosis (ABPA) showing central bronchiectasis

Diagnosis

The diagnostic criteria for ABPA in asthma and cystic fibrosis are same for adults and children. Rosenberg-Patterson criteria in 1977 included following eight characteristics: (1) asthma or cystic fibrosis; (2) peripheral blood eosinophilia ($> 1.0 \times 10^9/L$); (3) immediate cutaneous reactivity to AF antigen; (4) precipitating antibodies against AF antigen; (5) elevated total serum IgE ($> 1,000$ ng/mL); (6) Chest X-ray infiltrates (or history of), transient or fixed; (7) proximal bronchiectasis; and (8) elevated serum IgE and IgG antibodies (specific to AF antigen). Two years later, Nelson, et al in 1979 suggested at least five of the following seven criteria for diagnosing ABPA in CF patients, viz. wheezing, increased total serum IgE, positive specific IgE to *A. fumigatus*, serum *Aspergillus* IgG precipitins, positive skin test, radiological pulmonary infiltrates, and bronchiectasis. The recent criteria for diagnosis of ABPA in asthmatic patients as proposed by Greenberger is shown in **Table 1**. Recently, Cystic Fibrosis Foundation consensus had laid down diagnostic criteria of ABPA in cystic fibrosis as well as criteria for screening for ABPA in cystic fibrosis patients (**Table 2**). Diagnosis of ABPA in CF patients may be difficult as many clinical features, e.g., airway obstruction, pulmonary infiltrates, and bronchiectasis may be present in them even without ABPA.

Presence of *A. fumigatus* in sputum culture is nonspecific because patients with CF and even normal subjects without ABPA may harbor *Aspergillus*. IgE level is a useful disease activity marker and may be used in monitoring. Skin prick test is an important screening test for ABPA as it is uncommon in subjects

with negative result. Serum precipitins are neither sensitive nor specific. Recently, 22 recombinant *A. fumigatus* allergens (named from rAsp f1 to rAsp f22) have been identified and many of them may be useful for discriminating patients with *Aspergillus* sensitization from ABPA. Preliminary studies suggested that rAsp f2, f4, f6, and f16 may be specific for ABPA whereas rAsp f1 and f3 are nonspecific but it needs further research. Other serological markers, e.g., thymus and activation-regulated chemokine (TARC) and exhaled nitric oxide (NO) levels were also used to differentiate ABPA exacerbation from a bacterial exacerbation in CF patients.

Differential diagnosis includes uncontrolled asthma, foreign body inhalation, pneumonia, tuberculosis, immotile cilia syndrome, pulmonary infiltrates with eosinophilia, CF without ABPA, and sarcoidosis.

Management

Management of ABPA includes use of steroids for control of inflammation; and itraconazole to suppress *Aspergillus* colonization. Systemic corticosteroids are mainstay treatment for ABPA. Treatment is started with 0.5 mg/kg/day of oral prednisolone for 2–4 weeks with monitoring for clinical improvement and radiological clearance. After improvement from acute process, prednisolone (0.5 mg/kg) is given on alternate days for next 1–3 months and then tapered off over next 3 months while checking clinically and with serum IgE levels. Steroid dose is needed to increase, if IgE levels increases two folds or more. There is lack of evidence for or against the use of inhaled steroids and pulse methylprednisolone.

Table 1 Diagnostic criteria for allergic bronchopulmonary aspergillosis (ABPA) in asthma

Criteria	ABPA-central bronchiectasis	ABPA-seropositive
Essential criteria	<ol style="list-style-type: none"> 1. Asthma 2. Central bronchiectasis* 3. Immediate skin sensitivity to <i>Aspergillus</i> species or AF[#] 4. Total serum IgE conc.[§] > 417 kU/L (1,000 ng/mL) 5. Elevated serum IgE and/or IgG-AF 	<ol style="list-style-type: none"> 1. Asthma 2. Immediate skin sensitivity to <i>Aspergillus</i> species or AF 3. Total serum IgE conc. > 417 kU/L (1,000 ng/mL) 4. Elevated serum IgE and/or IgG-AF
Non-essential criteria	<ol style="list-style-type: none"> 1. Chest X-ray infiltrates 2. Serum precipitating antibodies to AF 	<ol style="list-style-type: none"> 1. Chest X-ray infiltrates

* Inner two thirds of chest CT field; [#] AF-*Aspergillus fumigatus*; [§] conc-concentration.

Adapted from Greenberger PA. Allergic bronchopulmonary aspergillosis. J Allergy Clin Immunol. 2002;110:685-92.

Table 2 Diagnostic criteria for allergic bronchopulmonary aspergillosis (ABPA) in cystic fibrosis

Criteria for classic case	Minimal diagnostic criteria	Criteria for screening for ABPA in CF
1. Acute/subacute clinical deterioration* not due to another etiology	1. Acute/subacute clinical deterioration* not due to another etiology	1. High index of suspicion for ABPA in patients > 6 years of age
2. Serum total IgE conc. [#] of $> 1,000$ IU/mL (2,400 ng/mL)	2. Serum total IgE conc. of > 500 IU/mL (1,200 ng/mL)	2. Test total serum IgE conc. annually. If it is > 500 IU/mL, test for immediate cutaneous reactivity or IgE antibody to AF
3. Immediate cutaneous reactivity to <i>Aspergillus</i> or presence of serum IgE antibody to AF [§]	3. Immediate cutaneous reactivity to <i>Aspergillus</i> or presence of serum IgE antibody to AF	3. If the total serum IgE conc. is 200–500 IU/mL, repeat the test, if there is increased suspicion for ABPA (disease exacerbation)
4. Precipitating antibodies to AF or serum IgG antibody to AF	4. One of the criteria 4 or 5, mentioned under classic case	
5. New or recent abnormalities on chest X-ray or CT, not cleared with antibiotics and physiotherapy		

*cough, wheeze, exercise intolerance, decline in pulmonary function, increased sputum; [#] conc-concentration; [§] AF-*Aspergillus fumigatus*.

Adapted from Stevens DA, Moss RB, Kurup VP, et al. Clin Infect Dis. 2003;37(Suppl 3):S225-64.

Itraconazole decreases the fungal burden and reduces inflammatory stimulus. Itraconazole is supposed to reduce the doses of steroids that are required along with decreased episodes of acute exacerbation in ABPA. Randomized controlled trials (RCTs) in asthmatic adults with ABPA suggest beneficial effect of itraconazole. There are no RCTs in CF patients with ABPA for use of itraconazole. Itraconazole is proposed for ABPA in CF patients based on observational studies. In children, usual dose of itraconazole is 10 mg/kg/day in two divided doses (maximum dose 400 mg/day). The total duration of therapy should be 3–6 months. Several other antifungal drugs (e.g., amphotericin B, ketoconazole, clotrimazole, nystatin and natamycin) have also been used for treatment of ABPA, but had adverse effects.

Anti-IgE therapy (omalizumab) is effective for allergic asthma but there is lack of evidence for efficacy in ABPA and further research is needed. Immunotherapy for ABPA in children is ineffective and may be risky and therefore, not recommended. Seasonal variation in ABPA may suggest beneficial effects of avoiding places with high burden of *Aspergillus* spores such as compost heaps and damp basements.

Prognosis

Early diagnosis before irreversible lung damage and prompt treatment ensure good prognosis. Prognosis of ABPA in CF patients also depends on progression of CF disease activity. Monitoring of radiological findings and IgE levels are important as clinical features are not so reliable for ABPA progression or remission.

PULMONARY ASPERGILLOMA

Pulmonary aspergillomas (commonly called fungal balls) are mass lesions of fungal hyphae proliferating without vascular invasion. They usually develop in pre-existing cavitory lesions, e.g., tuberculosis, abscesses, lung cysts, and histoplasmosis. Patients may develop fever, cough, and hemoptysis or may be asymptomatic and aspergillomas may be detected as incidental findings on chest imaging. Diagnosis is suggested by positive *Aspergillus* serology. Surgical removal is usual treatment with antifungals in certain subjects.

INVASIVE ASPERGILLOSIS

Invasive aspergillosis is caused by inhalation of conidia that proliferate into fungal hyphae and invade pulmonary vessels and tissue parenchyma. In majority of cases, *A. fumigatus* is responsible for IA. It occurs primarily in immunocompromised patients. Neutropenia, steroids therapy, cytotoxic chemotherapy, chronic granulomatous disease, transplantations, use of broadspectrum antibiotics and leukemia are important predisposing factors for IA. Lung is the most common primary focus, but hematogenous spread may occur to other organ systems. Incidence and prevalence of IA is not well studied in children.

Clinical Features

Patients with pulmonary IA present with fever, cough, and hemoptysis that persist despite use of broadspectrum antibiotics. Symptoms may vary because of underlying immune-deficient state and high index of suspicion is required for diagnosis. Radiological findings are nonspecific and may reveal characteristic *halo sign* (opaque rim around a nodule), *air crescent sign*, nodules, diffuse or lobar consolidation, hemorrhagic infarction and lung abscess.

Diagnosis

Diagnosis of IA is by biopsy and culture; but it may not be feasible to obtain tissue for diagnosis. Tissue-invasive hyphal forms in biopsy and positive culture are confirmatory of IA. Blood culture

and serum studies (because of poor immunological response secondary to underlying immunodeficiency) are not of much use. Bronchoalveolar lavage (BAL) may be of use and polymerase chain reaction (PCR) can further increase the yield. Galactomannan (a cell wall component of *Aspergillus*) based tests have some promise, though it may give false positive results in children receiving piperacillin/tazobactam. Detection of *Aspergillus* in pulmonary secretions (by staining or culture) along with clinical and radiological features is sufficient evidence for IA.

Treatment

Voriconazole is first line therapy for IA. Posaconazole, another azole antifungal, is an alternative drug. Amphotericin, either conventional or liposomal, are considered second line therapy now. Caspofungin is a newer antifungal agent having efficacy against IA. There is a lack of evidence to suggest usefulness of a combination of antifungal drugs for IA. Empirical antifungal therapy may be considered in certain high-risk group when IA is suspected clinically. Reconstitution of immune system by temporary stopping immunosuppressive agents and/or adding colony-stimulating factors is an adjuvant therapeutic modality.

IN A NUTSHELL

1. *Aspergillus* may cause hypersensitivity, saprophytic, or invasive disease in human.
2. Disease pattern of *Aspergillus* is determined by immune status of the individual, genetic susceptibility, and quantity and virulence of inhaled *Aspergillus*.
3. Allergic bronchopulmonary aspergillosis (ABPA) occurs in settings of asthma and cystic fibrosis.
4. High index of suspicion with early diagnosis of ABPA is crucial to start aggressive treatment for prevention of irreversible lung damage.
5. Oral prednisolone is the mainstay of treatment for ABPA in asthma and CF with itraconazole being a useful adjuvant therapy.
6. Invasive aspergillus is a notorious disease among immunosuppressed individuals, that needs early diagnosis and treatment.

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Chapter 33.5

Cryptococcosis

Ankit Parakh

Cryptococcosis is caused by fungi that belong to the genus *Cryptococcus*. *Cryptococcus* is found in the soil throughout the world, usually in association with large amounts of bird droppings. Cryptococcosis predominantly involves the central nervous system (CNS), lungs, skin, and bones, but other organs can also be affected. Although most cases occur in immunocompromised patients, the systemic disease may occur in seemingly immunocompetent individuals.

ETIOLOGY

Cryptococcus neoformans and *C. gattii* are basidiomycetous, encapsulated yeasts. *C. neoformans* and *C. gattii* can be sub-classified into four serotypes and two species with two varieties. The serotypes are based upon capsular agglutination reactions and are designated A, B, C, or D. Serotype A and D cryptococci were previously classified under the species *neoformans*. However, it has been proposed that the serotype A cryptococci be considered as a separate variety based upon genotypic differences. Serotype A cryptococci are now considered variety *C. grubii*; serotype D are classified under *C. neoformans* and they are divided into four molecular types (VNI, VNII, VNIII, VNIV). Serotypes B and C are now considered separately as *C. gattii*.

PATHOPHYSIOLOGY

Cryptococcal infection is usually acquired by inhalation of the fungal spores, although rarely cutaneous and ocular cryptococcosis has been reported with local inoculation. Infection in the immunocompetent host is usually limited to the lung. Pulmonary infection has a tendency toward spontaneous resolution and is frequently asymptomatic. Silent hematogenous spread to the brain leads to clusters of cryptococci in the perivascular areas of cortical gray matter, in the basal ganglia, and, to a lesser extent, in other areas of the CNS. In chronic cases, a dense basilar arachnoiditis is typical. Lung lesions are characterized by subpleural lesions, which contain yeast forms and have intense granulomatous inflammation.

CLINICAL PRESENTATION

Pulmonary Cryptococcosis

Although the lung is the most common portal of entry for infection, pulmonary cryptococcosis is uncommon in children. One-third of pulmonary infections are asymptomatic. Approximately, half of patients have cough or chest pain, and smaller percentages have sputum production (30%), weight loss (25%), fever (23%), and hemoptysis (20%). In Immunocompromised hosts, the onset may be more severe, and the course more rapid. Radiographic lesions in nonimmunosuppressed hosts include well-defined, noncalcified, single or multiple nodules, mass like infiltrates, hilar lymphadenopathy, pleural effusions, and lung cavitations. In immunosuppressed hosts, radiographic findings include poorly localized bronchopneumonia, lobar consolidations, alveolar and interstitial infiltrates.

Central Nervous System Cryptococcosis

Subacute or chronic meningitis is the most common manifestation of disseminated cryptococcal disease in children.

Meningitis occurs in more than half of cryptococcal infections affecting HIV-infected children. Headache, fever, nausea and vomiting are the usual symptoms. Neck rigidity is seen in 75% of patients who are not immunocompromised and in 33% of patients with HIV. Other, less frequent manifestations include alteration of consciousness, impaired mental function, cranial nerve lesions, visual deficits, papilledema, seizures, diplopia, focal neurologic deficits, photophobia, and abnormal cerebellar signs. The duration of symptoms before a diagnosis is established ranges from less than 1 week to 18 months and tends to be shorter in patients with HIV. The prognosis is better, if the disease is picked up early. Mortality is high up to 15–30%, especially in HIV-positive children. Relapses are described in immunocompromised children although rare with immunocompetent children. Postinfectious sequelae are common and include hydrocephalus, vision loss, cranial nerve deficits and seizures.

Cutaneous Cryptococcosis

Varied manifestations are described including ulcers, nodules, vesicles, abscesses, papules, and purpuric and sinus tracts. Skin lesions usually represent metastases to the skin of a disseminated infection, although local infections have been described. They can be difficult to diagnose clinically given the myriad presentations. Biopsy of the skin lesions with histological examination and culture is required.

DIAGNOSIS

High index of suspicion is required for diagnosis of *Cryptococcus* infections in children. Fever and headache in a child with known HIV or having risk factors for HIV suggest the possibility of *Cryptococcus*, *Toxoplasma* or CNS lymphoma. Evidence of a focal lesion on imaging is unusual in cryptococcal meningitis. In immunocompetent children, the diagnosis is difficult and is usually not considered. Child presenting with chronic meningitis should be evaluated for tubercular (TB) meningitis, *Acanthamoeba* and *Cryptococcus*. Cryptococcal meningitis is an important differential diagnosis in children with TB meningitis who are not responding to first-line anti-TB drugs. Lumbar puncture is the single most important test. Pleocytosis is seen in cerebrospinal fluid (CSF) but rarely exceeding 100 cells/mm³, glucose is reduced to less than 50 mg/dL, and proteins are raised. The findings are less pronounced in children with HIV. The samples should be subjected to direct smears with special stains, Cryptococcal antigen for rapid diagnosis and cultures.

C. neoformans may be shown by direct examination of clinical specimens from CSF, urine, sputum, bronchoalveolar lavage fluid, or aspirates of skin lesions using India ink preparations, Gram staining of smears of cytocentrifugated specimens, or special stains like mucicarmine and Masson-Fontana silver stains, which distinctively show the cell wall and the capsule of the organism.

During cryptococcal meningitis, the India ink CSF preparation reveals the yeast in 80% of cases in HIV-positive children and 50% of uninfected children. For rapid diagnosis of cryptococcal disease, especially meningitis, WHO has recommended the use of cryptococcal antigen tests; either latex agglutination or lateral flow assay should be used. These have a very high sensitivity and specificity. Serum can be tested for the same antigens, if CSF is not available. These are now being considered as point-of-care tests for diagnosis of cryptococcal meningitis. *C. neoformans* can be isolated in most routine mycologic or bacteriologic media, especially chocolate agar, Sabouraud agar and niger seed agar medium. The culture yields the organism in 87–100%.

TREATMENT OF CRYPTOCOCCAL DISEASE (TABLE 1)

The factors that need to be considered in guiding treatment of cryptococcosis are the degree of immunosuppression and extent of infection (pulmonary or extrapulmonary with and without meningitis). Limited data exists from pediatric literature and most of the recommendations are obtained from extrapolation of adult studies.

Treatment of Cryptococcosis in Immunocompetent Hosts

Central Nervous System Disease

For cryptococcal meningitis, a combination of amphotericin B (0.7–1 mg/kg/day), and flucytosine (100 mg/kg/day) is used as induction therapy for 2 weeks, followed by fluconazole (12 mg/kg/day) for 10 weeks. Alternatively, the amphotericin B and flucytosine combination may be continued for 6–10 weeks. The CSF should be examined after the first 2 weeks of therapy, at which time, 75% of patients have sterile CSF. A positive culture at this point is an indication for extending the treatment course beyond the minimum recommendation. Intraventricular and intrathecal amphotericin B may be needed for refractory cases. Lipid formulations of amphotericin B can be used in place of amphotericin B in patients with renal dysfunction, with similar therapeutic efficacy. Regardless of the initial regimen, some experts recommend a subsequent course of fluconazole, 3–6 mg/kg/day for 6–12 months. Treatment outcome is poor, if CNS disease is not recognized and treated early.

Pulmonary Disease

Pulmonary cryptococcal infection may resolve without treatment in immunocompetent hosts. These can be only observed; however, this approach should be considered only when the patient can be followed up closely. Most children however would need treatment given the potential for dissemination, the seriousness of CNS involvement, and the availability of effective and well-tolerated antifungal agents. Performing a lumbar puncture is mandatory in all cases of pulmonary

disease. Immunocompetent patients with asymptomatic and mild-to-moderate disease should be treated with fluconazole, 3–6 mg/kg/day for 3–6 months for asymptomatic disease or 6–12 months for mild-to-moderate disease. Itraconazole is an alternative drug though not preferred. If oral azoles cannot be taken, or progression of the disease occurs, amphotericin B, 0.4–0.7 mg/kg/day, is recommended. Severe pulmonary disease is treated similar to CNS disease.

Treatment of Cryptococcosis in Immunocompromised Hosts with AIDS

Cryptococcal Pneumonia

All HIV-infected patients with pulmonary cryptococcal infection must be treated because they are at high-risk for developing disseminated infection. For children with mild-to-moderate disease, treatment with fluconazole alone is appropriate and should be followed by prophylaxis. For patients with severe pneumonia, amphotericin B should be used until the patient is asymptomatic, at which time, fluconazole can be substituted for maintenance therapy. Patients with cancer and pulmonary cryptococcosis treated with fluconazole monotherapy generally had good outcomes.

Cryptococcal Meningitis

For meningeal cryptococcosis, induction therapy consists of a combination of amphotericin B (0.7–1.0 mg/kg/day) and flucytosine (100 mg/kg/day) for a minimum of 2 weeks. Induction is followed by consolidation treatment with fluconazole (12 mg/kg/daily) for a minimum of 10 weeks, or until CSF cultures are sterile. Because of the relapse rate of 50%, maintenance therapy is important after an acute episode of meningitis in HIV-infected individuals. Fluconazole given daily is the preferred drug for maintenance. Oral itraconazole or amphotericin B given one to three times weekly are alternative maintenance regimens.

Standard management principles of elevated intracranial pressure in children with cryptococcal meningitis include measurement of the CSF pressure and frequent therapeutic lumbar punctures. Neurosurgical procedures like ventricular shunting may be required in severe cases to control cerebral edema or hydrocephalus.

Table 1 Treatment of cryptococcal disease in children

Host	Site of disease	Primary	Secondary
Immunocompetent	Pulmonary or other extrapulmonary	Observation only might be considered Fluconazole, 3–6 mg/kg/day for 3–6 month for asymptomatic disease or 6–12 month for mild-to-moderate disease <i>Alternate:</i> Itraconazole	Amphotericin B, 0.4–0.7 mg/kg/day
	CNS	<i>Induction therapy:</i> Amphotericin B, 0.7–1 mg/kg/day with flucytosine, 100 mg/kg/day for 2 weeks; <i>Maintenance:</i> Fluconazole, 12 mg/kg/day for 10 weeks. <i>Alternate:</i> Amphotericin B and flucytosine combination for 6–10 weeks	Intraventricular and intrathecal amphotericin B may be needed for refractory cases.
Immunocompromised	Pulmonary or other extrapulmonary	All should be treated Fluconazole, 3–6 mg/kg/day for 3–6 m for asymptomatic disease or 6–12 m for mild-to-moderate disease <i>Alternate:</i> Itraconazole <i>Severe cases:</i> Amphotericin B, 0.4–0.7 mg/kg/day Fluconazole prophylaxis	Amphotericin B, 0.4–0.7 mg/kg/day
	CNS	<i>Induction therapy:</i> Amphotericin B, 0.7–1 mg/kg/day with flucytosine, 100 mg/kg/day for 2 weeks; <i>Maintenance:</i> Fluconazole, 12 mg/kg/day for 10 weeks. In case flucytosine is not available, use combination of amphotericin B and fluconazole <i>Alternate:</i> Amphotericin B and flucytosine combination for 6–10 weeks Fluconazole prophylaxis	Intraventricular and intrathecal amphotericin B may be needed for refractory cases.

Immune Reconstitution Inflammatory Syndrome

Immune reconstitution inflammatory syndrome (IRIS) has been described in adult and pediatric patients coinfecting with HIV and *C. neoformans* who are treated with highly active antiretroviral therapy (HAART). Patients with *C. neoformans*-related IRIS present with higher CSF opening pressures, glucose levels, and cell counts. Hence, immediate antiretroviral therapy (ART) initiation is not recommended in HIV-infected children with cryptococcal meningitis due to high risk of IRIS which might be life-threatening. ART initiation should be deferred until there is evidence of a sustained clinical response to antifungal therapy and after 2–4 weeks of induction and consolidation treatment with amphotericin B-containing regimens combined with flucytosine or fluconazole (after 2 weeks with nonmeningeal disease).

In children more than 5 years of age with successfully treated cryptococcal disease (meningeal and nonmeningeal), discontinuation of antifungal treatment maintenance is recommended, if the child had received prophylaxis for 1 year and has CD4 count more than 200 cells/mm³ (two measurements 6 months apart). In HIV-infected children aged between 2 years and 5 years, with successfully treated cryptococcal disease discontinuation of antifungal treatment maintenance is recommended, if the child is stable and adherent to ART and antifungal maintenance treatment for at least 1 year and with a CD4 cell count percentage greater than 25% or absolute count more than 750 cells/mm³ (two measurements 6 months apart). Maintenance treatment with should not be discontinued in children less than 2 years of age.

IN A NUTSHELL

1. Cryptococcosis is a fungal infection which predominantly involves the CNS, lungs, skin, and bones, but other organs can also be affected.
2. It usually affects immunocompromised children but can occur in immunocompetent children.
3. Subacute or chronic meningitis is most common manifestation of disseminated cryptococcal disease in children.
4. Cryptococcal antigen tests on CSF have a high sensitivity and specificity for diagnosis and now considered point-of-care tests.
5. Amphotericin B remains the drug of choice for induction followed by fluconazole for completion of therapy.

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Chapter 33.6

Coccidioidomycosis

James Homans, Yee Aye

Coccidioidomycosis is caused by two related fungi, *Coccidioides immitis* and *Coccidioides posadasii*, which have identical manifestations but different geographic distribution. *Coccidioides spp.* (heretofore, *Coccidioides*) are endemic only in the Americas, *C. immitis* in California, Baja California and Arizona, and *C. posadasii* in Arizona, Mexico and parts of Central and South America. Coccidioidomycosis has existed in the Americas since prehistory. It was first described by Posadas in Argentina in 1892 and recognized as a fungus by Ophuls and Moffitt in 1900. *Coccidioides* causes a wide range of disease in humans and domestic and wild mammalian species including dogs, cats, horses, rhinoceri, great cats and dolphins.

ORGANISM

Coccidioides species are found in areas that are hot and dry most of the year with intermittent periods of abundant rainfall. They are dimorphic fungi, assuming two forms depending on their environment (**Fig. 1**). In nature *Coccidioides* exist in saprobic form as soil molds while in animal hosts take a parasitic yeast-like form. The mold produces arthroconidia (arthrospores), hardy spores that break off from the parent mycelium and are transported on air currents. When airborne arthroconidia arrive in the tissue of an animal host, they germinate into spherules filled with endospores. When spherules rupture, endospores disseminate throughout the host, each one capable of producing a new spherule.

EPIDEMIOLOGY

Coccidioidomycosis usually occurs due to inhalation of arthroconidia but can also be inoculated percutaneously. Rarely exposure can occur nosocomially as by exposure to mold on a cast, and accidentally in laboratories. Coccidioidomycosis occasionally occurs outside of endemic areas due to exposure to fomites harboring arthrospores, or in travelers who have recently returned from endemic areas. Incidence and range of infection are increased in periods of increased airborne carriage such as storms and earthquakes, and with increased germination as after heavy rains.

The risk of coccidioidal infection depends on the intensity and duration of exposure. In endemic areas a large proportion of the population has evidence of past infection but only a small proportion has a history of symptomatic disease. Evidence of infection is highest among groups having the highest environmental exposure. However, even a brief exposure, such as car travel through an endemic area, can cause infection. It is thought that inhalation of a single arthrospore can lead to infection.

While risk of infection depends on exposure, the likelihood of developing severe or disseminated infection is affected by genetic predisposition as reflected by ethnic or racial group (Filipinos, African Americans and Hispanics have a markedly higher risk), immune status (deficient cell-mediated immunity leads to a higher risk), and sex (males have a higher risk). Extremes of age, pregnancy, poorly controlled diabetes mellitus, HIV infection, hematologic malignancies and immunosuppressive therapy increase the risk of severe coccidioidomycosis. Past infection usually leads to long-standing protective immunity. Patients with vigorous response to antigen exposure (coccidioidin) by positive skin test are less likely to develop severe disease. Children living

in endemic areas are at risk for infection and have risk factors for severe disease similar to adults. Congenital infection is rare.

PATHOGENESIS

Inhaled arthroconidia penetrate the alveoli and germinate into spherules. Their presence provokes a vigorous and complex immune response. Neutrophil migration and antibody production occur but are ineffective. Cell-mediated immunity, in particular TH1 response, is most important in control of infection. Similar to tuberculosis, there may be extensive extrapulmonary lymphohematogenous dissemination despite initial immunologic control. Tissue inflammation is mainly granulomatous sometimes with caseation.

CLINICAL FEATURES

Most coccidioidal infections are asymptomatic or have mild upper respiratory symptoms, 40% lead to self-limited flulike illness, characterized by cough, fever, malaise, myalgia, pneumonia, and maculopapular rash or erythema nodosum, 5% develop progressive pulmonary disease and 1% extrapulmonary disease.

Pneumonia

Pneumonia is almost always present in primary disease. *Coccidioides* is one of the causes of atypical pneumonia and is frequently misdiagnosed. Disease severity ranges from mild flulike illness to severe pneumonitis with adult respiratory distress syndrome (ARDS). Various infiltrate patterns can be present on chest radiograph including lobar, bronchoalveolar, reticulo-nodular, hilar adenopathy, thin-walled cavities and pleural effusion. A miliary pattern suggests lymphohematogenous seeding. In immunocompetent patients coccidioidal pneumonia frequently resolves without specific treatment. In some cases it may progress slowly to chronic pneumonia with fibrosis.

Extrapulmonary Manifestations

These are usually due to lymphohematogenous dissemination. The most frequently affected sites are skin, soft tissue, abdomen, bones and joints, and meninges. Meningitis and osteoarticular disease (involving tibia, vertebrae, skull, metatarsals and metacarpals) are difficult or impossible to eradicate. Draining fistulas may form. In contrast to pyogenic or tuberculous meningitis, coccidioidal meningitis progresses slowly. Fungemia is associated with high mortality. Reactivation of dormant infection can occur in immunocompromised patients.

APPROACH TO DIAGNOSIS

Clinical suspicion is essential for diagnosis of coccidioidomycosis. Skin testing with coccidioidal antigens is useful as an epidemiologic tool to detect past infection but not as a clinical test for current infection. Serologic testing is the mainstay of diagnosis. The usual test for established disease is *Coccidioides* complement fixation (CF), detecting IgG, which can be obtained on both blood and CSF. Anticoccidioidal IgG is not protective. Higher CF titers (greater than 1:16) suggest disseminated disease and should usually prompt antifungal treatment. Complement fixation titers can also be used to follow disease course. Detection of IgM antibodies is useful in the diagnosis of early disease. Immunodiffusion can also be used to detect either IgG or IgM but is time-consuming. Spherules and rarely mycelia can be detected in clinical specimens using fungal preparations (**Figs 2A to C**). *Coccidioides* grows readily on laboratory media from culture of clinical specimens. Definitive identification is by exoantigens or nucleic acid probes. Isolation of *Coccidioides* from a host with a consistent disease process is diagnostic.

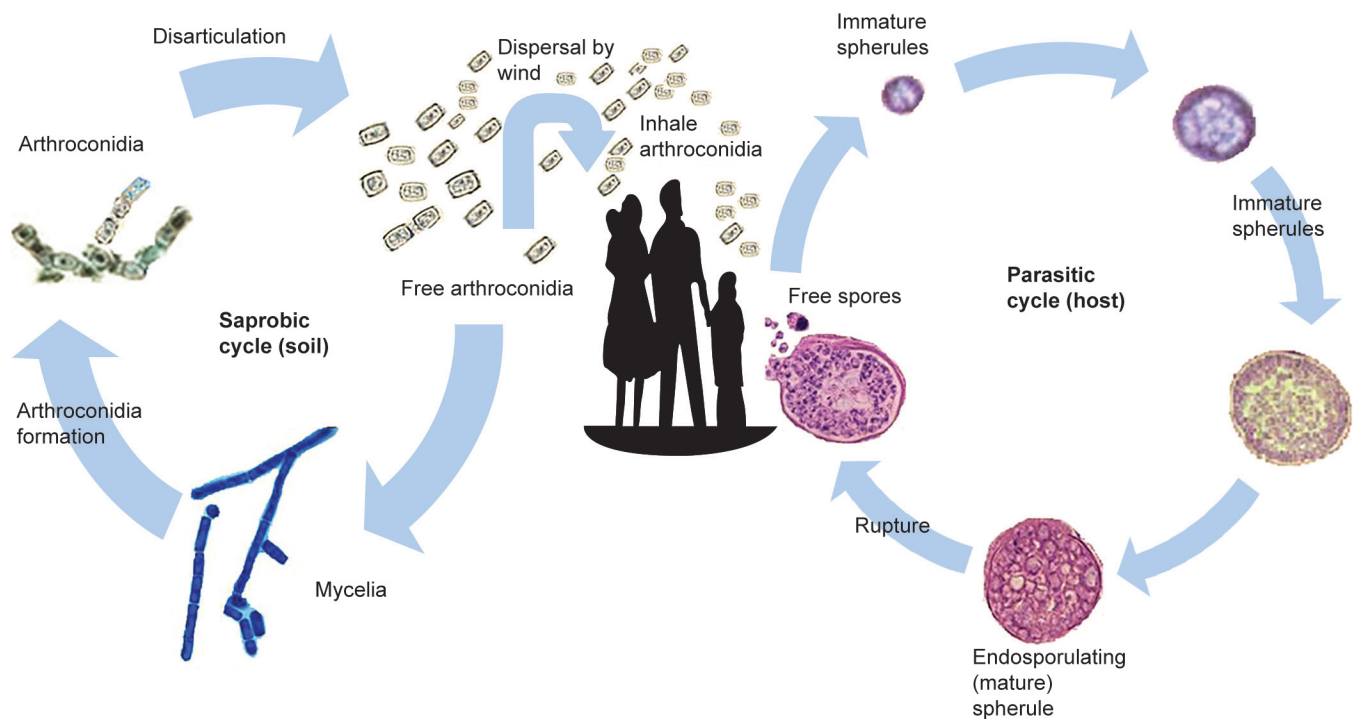
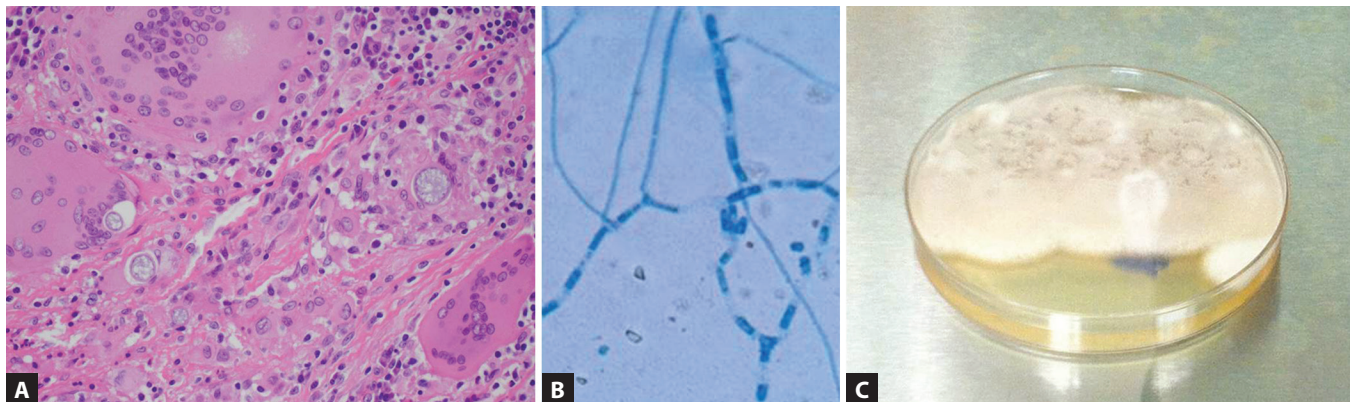


Figure 1 Schema of saprobic and parasitic phases of life cycle of *Coccidioides* spp.

Saprobic cycle: Hair-like mycelia with branching septate hyphae develop into arthroconidia (arthrospores). Arthrospores disarticulate into single arthroconidia (3–5 microns) and remain viable for long periods. In soil arthroconidia grow into mycelia and complete saprobic cycle. Wind and other events lift arthroconidia into the air where they can travel long distances. **Parasitic cycle:** Hosts (human, animals) inhale arthroconidia which change form into thick-walled structures called immature spherules. These mature and fill with endospores. They eventually rupture and release endospores. Each endospore can develop into a spherule completing the parasitic cycle



Figures 2A to C Specimens from a 19-year-old male coccidioidal lymphadenitis and pneumonia from excisional lymph node biopsy. (A) Hematoxylin and eosin stain demonstrating endosporulating *Coccidioides* spherules (1000X magnification); (B) Septate mycelium with arthrospore formation; (C) Culture of *Coccidioides immitis* showing floccose grayish-white colony

Source: Dr Rosemary She

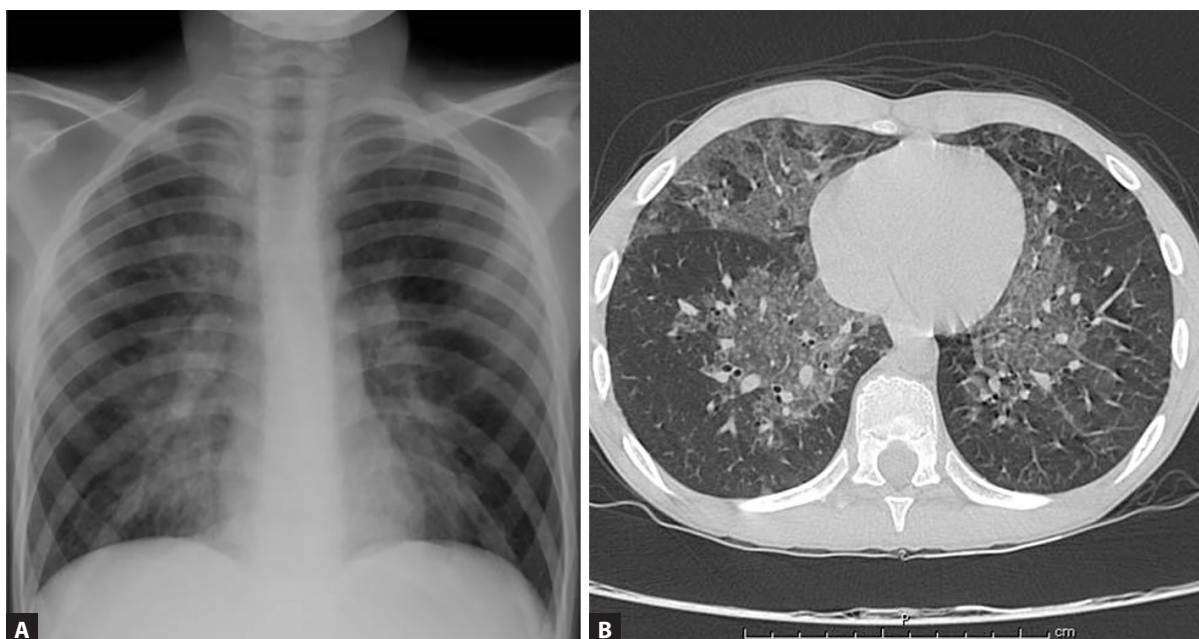
Pneumonia

Chest radiograph can show various patterns, but reticulonodular infiltrates, thin-walled cavities and hilar adenopathy are suggestive (**Figs 3A and B**). Culture of sputum, endotracheal aspirate or bronchoscopy specimen, will frequently grow *Coccidioides*. Serologic testing supports the diagnosis if positive but should not be relied upon for exclusion.

Meningitis

Diagnosis of coccidioidal meningitis relies on clinical suspicion, radiologic studies, and appropriate testing of CSF. Opening pressure

should be performed. Lumbar CSF in coccidioidal meningitis will usually show pleocytosis (50–200/mm³) with lymphocyte predominance, markedly elevated protein and decreased glucose (**Table 1**). Eosinophilia is frequently present. CSF serology is not sensitive enough to exclude disease. Presence of fungal elements, spherules or hyphal elements, on CSF microscopy is suggestive of a high fungal burden. Positive CSF serology (usually CF) or culture for *Coccidioides* is diagnostic. Brain imaging by CT or MRI may range from normal to obstructive hydrocephalus with transependymal edema.



Figures 3A and B A 14-year-old male with coccidioidal pneumonia. (A) Chest radiograph shows bilateral interstitial lung disease and hilar prominence. Right upper lobe opacity may represent atelectasis; (B) Computerized tomography (CT) scan shows ground glass attenuation throughout all lobes of lungs with a central prominence

Source: Dr Linda Vachon

Table 1 Typical cerebrospinal fluid (CSF) findings in children with meningitis caused by *Coccidioides* and other microorganisms

CSF	Cell count (WBC/mm ³)	Neutrophils	Predominant cell types	Protein (mg/dL)	Glucose (mg/dL)	Stain	Comment
Normal	0–20‡	0–5%	Lymphocytes or monocytes	< 45£	2/3 of serum	No organisms	Several PMNs in a neonatal patient's CSF can be normal
Coccidioidal	< 500	< 10–20%	Lymphocytes, monocytes sometimes eosinophils	> 100–200	< 1/2 of serum	Rarely spherules or hyphal elements	
Fungal	< 500	< 10–20%	Lymphocytes, monocytes	> 100–200	< 1/2 of serum	Rarely hyphal elements	<i>Cryptococcus</i> , histoplasmosis, blastomycosis
Tuberculous	< 500	< 10–20%	Lymphocytes, monocytes	> 200–300	< 1/2 of serum	AFB stain rarely positive	May have mononuclear cells predominance
Viral	100–1,000 (mostly < 500)	20–40%	Lymphocytes	N or < 100	N or < 1/2 of serum	No organisms	PMNs predominate early in course
Bacterial	1,000–5,000 (range < 100 to > 10,000)	> 50–90%	PMNs	> 100–500	< 1/2 of serum	Gram stain sometimes positive	< 500 WBC/mm ³ can be seen in severe or rapid onset pneumococcal meningitis

Abbreviations: CSF, cerebrospinal fluid; WBC, white blood cells; PMNs, polymorphonuclear leukocytes; N, normal

‡ Normal CSF may contain up to 30 leukocytes/mm³ in newborn

£ CSF protein may have up to 150 mg/dL in neonate

Osteomyelitis

Coccidioidal osteomyelitis is suggested by radiologic evidence of bone inflammation or destruction, usually radiolucencies, in a patient with known or suspected coccidioidal infection. Radiological features are shown in **Figures 4A to C**. Confirmation is by demonstration of spherules in biopsy or growth of *Coccidioides* on culture of biopsy material.

MANAGEMENT (TABLE 2)

The first step in the management of primary coccidioidomycosis is deciding whether to treat. Though not proven to be effective in preventing severe disease, treatment of immunocompetent patients with primary coccidioidomycosis should be considered, especially those in high-risk demographic groups. Immunocompromised patients with primary infection should be given a course of antifungal treatment to prevent severe disease.



Figures 4A to C X-rays from 9-year-old boy with multifocal coccidioidal osteomyelitis with fistulous tracts. (A) Expansile lytic lesion in left fourth middle phalanx with cortical destruction and adjacent soft tissue swelling; (B) Lytic lesion in right femoral epiphysis medially with adjacent soft tissue swelling; (C) Lytic lesion in right calcaneus bone at distal heel with adjacent soft tissue swelling

Source: Dr Linda Vachon

Table 2 Medical and surgical management of coccidioidal disease

Disease process	Medical management	Treatment of fulminant or rapidly progressive infection	Salvage therapy	Surgical management	Estimated duration of therapy
[§] Primary coccidioidomycosis	May not require treatment but consider on case-to-case basis				Observation for 6–12 months
Progressive or complicated pulmonary	Itraconazole Fluconazole	Amphotericin (Ampho) B followed by azole Ampho B + azole	Voriconazole Posaconazole	Ruptured cavity Persistent or enlarging nodules symptomatic cavity, Empyema hydro-pneumothorax	3–6 months Chronic, diffuse cases may treat ≥ 12–24 months
Lymphadenitis	Fluconazole Itraconazole	Ampho B followed by azole	Voriconazole Posaconazole		3–6 months if persists, may treat up to ≥ 12–24 months
Disseminated (non-meningeal)	Fluconazole Itraconazole	Ampho B followed by azole Ampho B + azole	Voriconazole Posaconazole Caspofungin Caspofungin + Fluconazole Caspofungin + Voriconazole		≥ 6 months; For refractory cases ≥ 12–24 months
Skin and soft tissue	Fluconazole Itraconazole	Ampho B followed by azole	Voriconazole Posaconazole		3–12 months
Musculoskeletal	Itraconazole [¶] Fluconazole	Ampho B followed by azole Intra-articular ampho B + azole	Voriconazole Posaconazole	-High CF titer (≥ 1:128) Extensive destructive lesions, large abscesses, progressive tissue destruction, bony sequestrations, vertebral instability, or impingement on critical organs	Range 6–12 to 24 months
Meningitis	Fluconazole Itraconazole	Ampho B + azole Intrathecal ampho B +/- azole	Posaconazole Voriconazole	Obstructive hydrocephalus May require ventriculo-peritoneal shunt	Lifelong with azoles

[§]Healthy patients without evidence of extensive coccidioidal infection or risk factors for more serious infection may not need antifungal therapy. However, it is important that such patients be followed for a year or longer to monitor for the development of complications.

[¶]Osteoarticular infections may respond better to itraconazole treatment than to fluconazole treatment.

Medical Treatment

Treatment of coccidioidomycosis relies on antifungal drugs with appropriate surgical interventions. Amphotericin B, including lipid-based preparations, remains the drug of choice in severe pneumonia or disseminated disease. Fluconazole is an excellent treatment for both systemic and meningeal disease due to excellent anticoccidioidal activity, excellent oral and intravenous bioavailability, excellent meningeal penetration and a favorable toxicity profile. Itraconazole is possibly superior to fluconazole for treatment of nonmeningeal disease. Voriconazole and posaconazole have also been reported effective in refractory cases with fluconazole resistance. Echinocandins have been used in refractory cases.

Surgical Treatment

Surgical intervention is frequently necessary in the management of coccidioidomycosis. The most common interventions include incision and drainage/debridement of abscesses and infected bone and joints. In some cases, reconstructive surgery becomes necessary. CSF diversion by ventriculoperitoneal shunting is frequently necessary in obstructive hydrocephalus.

PROGNOSIS

Most coccidioidomycosis can be managed effectively. Most nonmeningeal disease can be cured with adequate courses of antifungals and judicious surgery to drain abscesses and remove infected tissue. Patients with incurable disease can be maintained on suppressive therapy for many years. Immunocompromised patients may have more severe initial disease, are more difficult to treat and have poorer outcomes.

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IN A NUTSHELL

1. Likelihood of coccidioidal infection depends on level and duration of exposure, while likelihood of developing coccidioidal disease depends on patient characteristics including genetic predisposition, age, sex, pregnancy and immune status.
2. Most coccidioidal infections are asymptomatic or minimally symptomatic and resolve without treatment.
3. *Coccidioides* species can cause severe pulmonary and extrapulmonary infections including pneumonia, adult respiratory distress syndrome (ARDS), fungemia, septic shock, meningitis, osteomyelitis and, septic arthritis.
4. Diagnosis of coccidioidal infection entails a high index of suspicion, astute clinical evaluation, appropriate radiologic studies, appropriate laboratory studies such as serologic testing for IgG and IgM of blood or CSF, fungal stain and culture of clinical specimens, in some cases polymerase chain reaction (PCR) or other molecular techniques.
5. Treatment of coccidioidal infection entails antifungal therapy with azole antifungals or amphotericin B preparations, respiratory and hemodynamic support in severe cases, and judicious surgical intervention.

Chapter 33.7

Blastomycosis

G Raghurama Rao

Blastomycosis is a relatively uncommon chronic mycosis caused by inhaling conidia of the dimorphic fungus, *Blastomyces dermatitidis*. All age groups are susceptible to blastomycosis. There are three clinical forms of the disease: pulmonary, disseminated and primary cutaneous blastomycosis.

THE AGENT

Blastomyces dermatitidis exists in nature as a mold. In human and animal tissues it forms large, round budding yeast cells. The natural habitat of *B. dermatitidis* is the soil. Higher soil temperatures and recent rainfall facilitate growth of the fungus. *B. dermatitidis* also occurs in decaying wood and other organic materials including bird guano and animal excreta, forest or sandy soils, water ways, ponds and river banks.

EPIDEMIOLOGY

Blastomycosis is endemic in the South Eastern and South Central United States and Great Lake region. It was originally referred to as North American blastomycosis but the term is misleading as *B. dermatitidis* has a worldwide distribution. Cases of blastomycosis have been documented in at least 15 African countries as well as in Europe, South America, the Middle East, South Asia and India. In India, blastomycosis is a rare disease. The first case of blastomycosis was reported from Uttar Pradesh in 1983. Thereafter, several cases of blastomycosis in humans and animals have been reported mainly from the states of Uttar Pradesh, Delhi, Madhya Pradesh, Tamil Nadu, Karnataka and Andhra Pradesh. There is no well-defined endemic area of blastomycosis in India.

Host factors *Blastomyces dermatitidis* infection was formally thought to be more prominent in men, but women are also equally affected. All age groups are susceptible but majority of the patients are in 20–70 age groups. Children constitute 3–10% of total cases of blastomycosis. Two patients in the perinatal period have been reported. Recently one case of disseminated blastomycosis in a 4-year-old boy and another case of cutaneous blastomycosis in an 8-year-old boy were reported from Andhra Pradesh and Delhi, respectively. In India, these cases are usually mistaken for tuberculosis and under reported. The disease often occurs in individuals with an outdoor occupation such as construction or farming or recreational interest or playing in the dusty atmosphere. In contrast to other fungal infections usually seen in immunocompromised patients, as an opportunistic infections, *B. dermatitidis* is a true pathogen and often affects immunocompetent individuals.

PATHOGENESIS

Inhalation of *B. dermatitidis* spores is the usual mode of infection in humans. Occasional cases have followed traumatic cutaneous inoculation. Other uncommon ways of transmission are transplacental infection of newborn, postmortem transmission at autopsy and venereal transmission. The median incubation period for inhalation (pulmonary) blastomycosis ranges from 30 days to 40 days and for primary cutaneous blastomycosis is 14 days.

Following inhalation, conidia transform into yeasts and induce an inflammatory response with mixed abscess or granuloma in the alveoli. Alveolar macrophages can inhibit the transformation of conidia into yeasts and neutrophils are also active. The process is further influenced by lung surfactant in a complex interplay of

local factors of immunity. T-lymphocytes are the chief mediators of immunity to *B. dermatitidis*. Especially, the Th1 response is primarily responsible for effective immunologic control of infection. The humoral immune system is not significant. Yeasts are relatively resistant to phagocytosis and killing. The BAD-1 (blastomycetes adhesion 1) yeast cell wall protein mediates cellular adhesion and is an indispensable virulence factor and the main target for cellular and humoral immunity. BAD-1 suppresses phagocyte release of TNF- α through transforming growth factor- β -dependent and independent mechanisms. Melanin, another virulence factor, protects the fungus from the leukocyte oxidative burst. Dissemination of the disease to the other organs from the primary pulmonary infection can be through blood stream or lymphatics.

CLINICAL FEATURES

Clinical manifestations range from a transient pulmonary infection to chronic pulmonary infection or to more wide spread disseminated disease. In children, lung involvement is followed by that of skin, bone, subcutaneous masses and central nervous system in descending order of incidence.

Pulmonary Blastomycosis

Infection typically occurs by inhalation. Most infections are asymptomatic and resolve without treatment.

Acute pneumonia About 50% of individuals exposed to *B. dermatitidis* spores develop an acute symptomatic flu-like illness characterized by fever, chills, productive cough, myalgia, arthralgia, pleuritic chest pain and weight loss. The radiological findings are nonspecific and include lobar or segmental consolidation, often in the lower lobes. Most of the patients recover after 2–12 weeks of symptoms. Patients with miliary disease, diffuse pneumonitis, or acute respiratory distress syndrome have a mortality of 50–89%. Others with acute blastomycosis fail to recover and develop a chronic pulmonary infection or disseminated infection.

Chronic pneumonia It is the most frequent presentation, with nodular and lobar infiltrates and the symptoms are similar to those of tuberculosis. Spontaneous resolution is unusual. The radiological findings include consolidation, fibronodular interstitial infiltrate, mass lesions, pleural thickening and pleural effusions. Cavitation is uncommon. In immunocompromised patients blastomycosis may cause severe pulmonary disease with high mortality. Up to 80% of patients with pulmonary blastomycosis manifest with skin lesions.

Cutaneous Blastomycosis

The skin and subcutaneous involvement is the second most common manifestation of blastomycosis and is seen in approximately 60% of patients. Although there are reports of disease due to direct inoculation, skin involvement is usually the result of secondary dissemination following lung infection. The lesions tend to be painless and present either as raised verrucous lesions with irregular border or as ulcers (**Fig. 1**). The former, which are more common, begin as small maculopustular lesions that slowly spread to form large nodular or papulonodular lesions with heaped-up borders. These lesions appear on exposed sites, such as face, neck or extremities and can be mistaken for squamous cell carcinoma or other chronic cutaneous infections like tuberculosis. Besides the skin, ulcerative lesions can appear on the mucosa of the nose, mouth and throat.

Primary cutaneous blastomycosis is very rare. Direct cutaneous inoculation manifests as a chancre at the trauma site, sometimes with associated lymphangitis and lymphadenitis which is typically absent in cases of secondary cutaneous blastomycosis. Local lymph nodes are involved in 65% cases. A mixture of verrucous lesions, ulcers, nodules and papules may be seen in primary cutaneous blastomycosis.



Figure 1 Multiple verrucous plaques of blastomycosis

Others

Osteomyelitis occurs in about 30% of patients with disseminated blastomycosis. The spine, ribs and long bones are the most common sites of infection. Arthritis occurs in up to 10% cases. Meningitis and spinal or brain abscess is rare and seen in 1–5% cases of disseminated blastomycosis. Adrenal glands, thyroid, liver, spleen and gastrointestinal tract are sometimes involved. Choroiditis and endophthalmitis have been reported. Blastomycosis in immunocompromised patients carries a high mortality.

DIFFERENTIAL DIAGNOSIS

Tuberculosis of the lung, skin, bone or genital tract, coccidioidomycosis, histoplasmosis of the lung, bone or meninges and mucocutaneous paracoccidioidomycosis and other infections that can be confused with blastomycosis.

DIAGNOSIS

Microscopic examination is a reliable means to identify characteristic broad-based budding of *B. dermatitidis* in tissue wet mounts of the sputum or exudates following potassium hydroxide (KOH) preparation. Culture on Sabouraud's dextrose agar is the gold standard for isolation and identification of the fungus. The diagnosis can also be made by demonstration of budding yeasts on cytopathology or histology of affected tissue. Skin biopsy specimens from cutaneous blastomycosis show pseudoepitheliomatous hyperplasia with intraepidermal microabscess formation and occasional intraepidermal blastomycetic cells. Poorly defined granuloma with multinucleated giant cells with broad based yeast forms is also seen (**Fig. 2**). Complement fixation, immunodiffusion and enzyme-linked immunosorbent assays have low sensitivity and specificity and are not useful.

TREATMENT

Amphotericin B (0.7–1 mg/kg/day) is the drug of choice for newborns and children with severe blastomycosis. Treatment is continued for 1–2 weeks or until improvement is noted, followed by oral itraconazole 10 mg/kg/day (up to 400 mg/day) as step-down therapy, for a total of 12 months. Children with mild to moderate

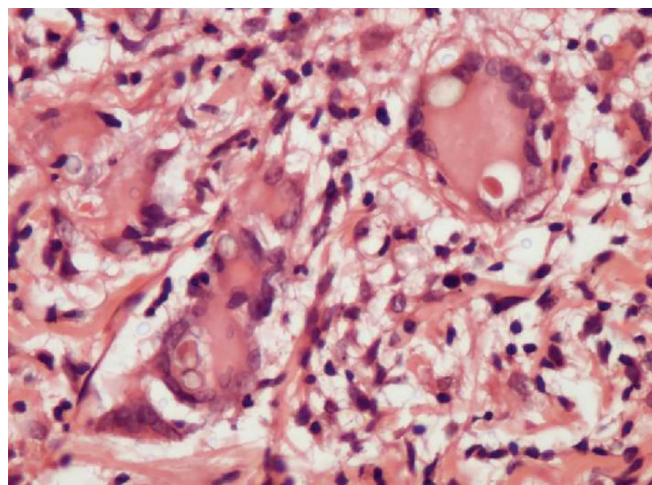


Figure 2 Multinucleated giant cells with fungal yeast forms

blastomycosis can be treated with oral itraconazole (10 mg/kg/day to a maximum of 400 mg orally per day) for 6 months.

PROGNOSIS

Excellent clinical response (> 90%, with few relapses) is achieved with itraconazole at 200 mg/day for 6 months in immunocompetent patients. Amphotericin B affords cure rates of 97% in uncomplicated disease.

IN A NUTSHELL

1. Blastomycosis is caused by inhalation of spores of dimorphic fungus, *Blastomyces dermatitidis*.
2. There are 3 clinical forms: pulmonary, disseminated and primary cutaneous.
3. The most common organs involved are the lungs, skin, bone and CNS, in that order.
4. Diagnosis is by demonstration of fungus in the tissue, sputum and exudates by potassium hydroxide (KOH) mounts and culture.
5. Amphotericin B is the drug of choice in severe cases and oral itraconazole for mild cases.

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Chapter 33.8

Histoplasmosis

S Nivedhana, S Balasubramanian

Histoplasmosis is a systemic granulomatous disease caused by dimorphic fungus *Histoplasma capsulatum*. It is an endemic mycosis and is the most common pulmonary and systemic mycosis throughout the world. The first case was described by Samuel Taylor Darling in 1905, in whose honor it was designated as *Darling's disease*. He named it after observing the intracellular yeasts within the macrophages (histiocytes) which resembled *Plasmodium* and appeared to have a capsule.

EPIDEMIOLOGY

The disease is prevalent worldwide in areas of temperate climate and is endemic in USA, Latin America and Africa. In India majority of cases are reported from eastern and northeastern parts along the gangetic plains. Two distinct varieties of *H. capsulatum* are pathogenic to humans:

1. *H. capsulatum* var. *capsulatum*—distributed worldwide causing classical or small form histoplasmosis
2. *H. capsulatum* var. *duboisii*—restricted to sub-Saharan Africa causing African or large-form histoplasmosis.

The infection is common in rural areas amongst adult men but in children there is no such sex predilection. The soil with high nitrogen content related to droppings of chicken, bats and high humidity acts as the reservoir and the source of infection. The fungi exist in the soil in mold or filamentous form. Man to man transmission is rare. In India the condition might be under diagnosed due to lack of awareness or misdiagnosed as tuberculosis.

PATHOGENESIS

The fungi are inhaled as conidia from the soil and become unicellular yeasts in alveolar macrophages. The yeasts evade the host immune response by attaching to integrin cell surface receptors, enter the neutrophils and macrophages and after altering the intracellular environment, replicate inside them. Successful clearance of infection depends on intact cell-mediated immunity (CMI) and cytokines (TNF- α , IFN- γ , IL-1, IL-4 and IL-12).

If the disease establishes there is extensive granulomatous inflammation with formation of caseating and noncaseating granulomas. Individuals with primary or acquired cellular immunodeficiencies and infants are at higher risk of dissemination to all phagocytic cells of reticuloendothelial system including liver, spleen, bone marrow and lymph nodes. There is frequent bilateral adrenal enlargement. Histopathology of CNS lesions includes granulomatous basilar meningitis and vasculitis.

CLINICAL FEATURES

The infection is asymptomatic in majority of immunocompetent individuals. This is common in endemic areas and is indicated by positive histoplasmin skin test without any focus of infection. Classification of symptomatic infection is based on duration of infection and site of involvement as follows.

Acute Pulmonary Histoplasmosis

Among symptomatic cases, most infections are mild, self-limited with an influenza like illness which resolves in 3–5 days. After exposure to large inocula the symptoms include fever, chills, myalgia, and persistent cough for 2 weeks. If it lasts longer there is weight loss, fatigue and recurrent nonpleuritic chest pain. There might be dyspnea

in diffuse pneumonitis. Complications include mediastinal adenitis, mediastinal granuloma, obstruction of mediastinal structures by enlarged lymph nodes, pericarditis, and mediastinal fibrosis. At later stages, these may be accompanied by acute migratory polyarthritides, erythema multiforme or erythema nodosum.

Chronic or Cavitory Pulmonary Histoplasmosis

This presentation is rare in children. There is formation of apical or subapical cavities with hemoptysis. There may be formation of pulmonary histoplasmoses—granulomas encased in dense fibrous tissue with concentric layers of collagen tissue and subsequent calcification. These enlarge to a size of 3–4 cm over several years and can radiologically mimic pulmonary neoplasms. If left untreated the disease is fatal.

Primary Cutaneous and Mucocutaneous Histoplasmosis

Petechiae or ecchymotic purpura are seen over skin of the abdomen or thorax. In Indians, localized oral cavity ulcers (Fig. 1) are more frequent than pulmonary lesions and skin lesions are found only in few.

Progressive Disseminated Histoplasmosis

This complication occurs in immunodeficient patients and especially in children under 2 years of age. Transplacental infection has also been documented in infants born to women with progressive disseminated histoplasmosis (PDH) complicating AIDS. PDH may either result from exogenous exposure (most common) or reactivation of quiescent endogenous infection. PDH in adults can be classified as acute, subacute or chronic but in children it is always acute, progressive and life-threatening infection. The histoplasmin skin test is negative in children who develop PDH subsequently.

Progressive Disseminated Histoplasmosis of Infancy

The presenting symptoms are fever, cough, oropharyngeal ulcers, tachypnea, lymphadenopathy, hemorrhagic skin lesions, and gastrointestinal bleeding. Hepatosplenomegaly is always present. The lymph nodes, bone marrow, adrenals, and gastrointestinal tract are commonly involved. There is pancytopenia, and disseminated intravascular coagulation owing to extensive involvement of reticuloendothelial cells simulating lymphoreticular malignancy. With appropriate antifungal therapy, survival is excellent.



Figure 1 Oral ulcers in histoplasmosis

Reproduced with permission from Chande C, Menon S, Gohil A, et al. Cutaneous histoplasmosis in AIDS. Indian J Med Microbiol. 2010;28:404-6.

Progressive Disseminated Histoplasmosis in Immunocompromised Hosts

This presentation is seen in patients with immunodeficiency disorders, organ transplantation, chronic renal failure and those on immunosuppressive therapy for hematologic malignancies. In children on chemotherapy PDH occurs as remission or relapse. They present with persistent fever and tachypnea. Chest X-rays show diffuse interstitial infiltrates and there is progressive hypoxemia. But the same clinical picture can also be caused by *Pneumocystis*, cytomegalovirus (CMV) and other opportunistic viral and fungal infections. In the GI tract distal ileum is commonly involved, followed by colon and stomach. These patients usually present with bloody diarrhea, gastrointestinal bleeding and perforation. Meningitis occurs in majority of infants with PDH. In adults, CNS infections manifest as cerebral abscess or chronic meningitis.

Diagnosis is established by *Histoplasma* antigen assay of urine. In cases where the assay is negative, lung biopsy is useful which is also most sensitive and specific. Bronchoalveolar lavage (BAL) fluid examination is useful in adults but not in children.

Progressive Disseminated Histoplasmosis in HIV Patients

Histoplasmosis is an AIDS defining illness and patients with CD4 counts less than 150/ μ L are at increased risk. Prior to the development of highly active antiretroviral therapy (HAART), disseminated disease was present in most of AIDS patients. Gastrointestinal and CNS infection is common in adults. There are only few reports of histoplasmosis in HIV infected children. In AIDS patients with histoplasmosis receiving HAART an immune reconstitution inflammatory syndrome (IRIS) has been described.

Other Infections

CNS symptoms occur in few adults with PDH and include meningitis, encephalitis, cranial nerve palsies and stroke. They are unusual in immunocompetent children. Disseminated meningitis is reported in children with PDH of infancy. *Presumed ocular histoplasmosis syndrome* is a late sequelae of subclinical infection. It is characterized by choroidal scars in macula (histo spots), peripapillary atrophy, and choroidal neovascularization which can lead to loss of central vision. This is rare in children. *African histoplasmosis* has higher tendency to involve bones (skull, ribs) with osteolytic lesions, followed by skin (cutaneous ulcers, papules and nodules) and subcutaneous granulomata and abscess with discharging sinuses. There is lesser frequency of lung or internal organ involvement.

DIFFERENTIAL DIAGNOSIS

Clinical features closely mimic that of tuberculosis. However, radiologically calcification is more common in histoplasmosis than TB. Intracellular yeasts of *Histoplasma* can be confused with *Leishmania donovani* (differentiated by the presence of kinetoplast) and *Toxoplasma gondii* (differentiated by the presence of tachyzoites of *T. gondii*, which are not stained with fungal stains). In tissue sections of AIDS patients *Penicillium marneffei* resembles *Histoplasma* but is differentiated by the presence of transverse dividing fission cells in the former.

DIAGNOSIS

Imaging

The chest radiographs in adults shows small, nodular lesions with enlarged hilar nodes and pulmonary infiltrates. Calcification is seen in later stages. CT scan is more sensitive and clearly delineates parenchymal lesions. Abdominal ultrasound or CT shows bilateral adrenal enlargement in adults. Generally in children, radiographic

findings are not pathognomonic. In radiographs of children with PDH with immunosuppression, diffuse interstitial infiltrates are commonly seen that worsen rapidly with progressive hypoxemia.

Microscopy and Culture

The specimens helpful are sputum, bone marrow, CSF, body fluids, lymph node aspirate/biopsy and blood smears. KOH mount can miss out on tiny yeast cells. With Giemsa staining, the fungus appears as tiny, oval yeasts (2–4 μ) within macrophages and neutrophils. The GMS (Gomori methenamine silver) stain is particularly sensitive as calcification artifacts are dissolved during staining. *Histoplasma* can be cultured onto Sabouraud dextrose agar. Most isolates grow in 3–4 weeks. At 25°C the mycelium grows as fluffy, aerial mycelium that is white or buff brown. On lactophenol cotton blue (LPCB) mount, septate hyphae with small, elliptical microconidia (2–4 μ) are seen laterally attached to the hyphae. Prominent thick walled, tuberculate macroconidia (8–16 μ) are seen from short conidiophore (**Fig. 2**). The sensitivity of culture varies from 40% in acute to 85% in disseminated histoplasmosis. Lysis-centrifugation system is used for recovery of *Histoplasma* from blood and the resulting concentrate is inoculated onto Sabouraud dextrose agar, which shortens the time for growth from 16 days to 9 days.

Antibody Detection

Serological tests become positive usually after 4 weeks of exposure. The antigens used are derived from merthiolated suspensions of whole yeast cells (Y) in saline and mycelial form (M) culture filtrate (H-histoplasmin).

Complement fixation (CF) test Single titer of 1:32 or higher or fourfold increase between acute and convalescent sera is suggestive of recent infection. The CF-Y phase is more sensitive than CF-M phase in recent infection. CF-M phase is more sensitive and specific for diagnosis of isolated meningitis in histoplasmosis.

Micro-immunodiffusion (ID) Detects precipitins against M and H glycoprotein antigens. More specific than CF. Not approved for use in cerebrospinal fluid (CSF) samples. The H band is seen infrequently and it suggests active infection. It is seen less consistently in children. The M band is present in both active and chronic histoplasmosis.

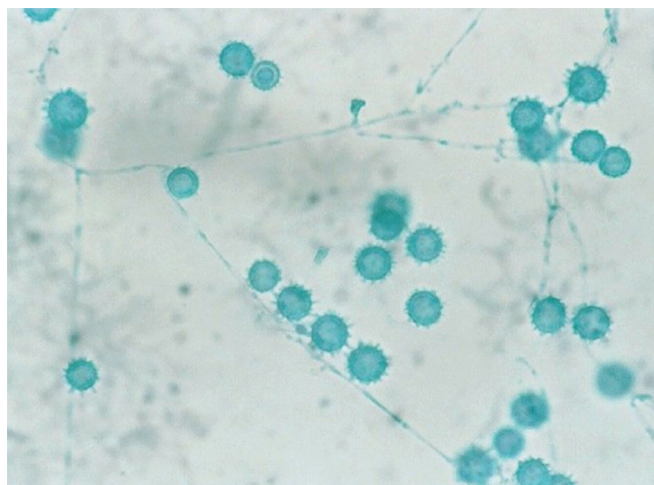


Figure 2 *Histoplasma capsulatum* lactophenol cotton blue (LPCB) mount: Showing tuberculate macroconidia. Reproduced with permission from Baradkar VP, et al. A rare case of *Histoplasma fungemia* in an AIDS patient. Indian J Med Microbiol. 2011;29: 188-91.

Antigen Detection

These are rapid, accurate and noninvasive method for diagnosis of histoplasmosis from serum, urine, CSF and BAL fluid samples. The sensitivity varies from 75% to 81% in acute pulmonary histoplasmosis to 92% in PDH. Extremely useful in immunocompromised patients in whom serological tests are often negative. Utilizes quantitative, third generation enzyme-linked immunosorbent assay (ELISA). Levels should be measured before the start of therapy, at 3–4 months interval during therapy and at the end of therapy. Antigen levels in serum and urine reduce with treatment and become absent after adequate treatment. In cases of relapse, monitoring antigen levels for 1 year is necessary.

Cross reactions may be seen with paracoccidioidomycosis, blastomycosis, penicilliosis marneffeii and African histoplasmosis. False-positive results occur with body fluids containing high protein (pleural, pericardial, peritoneal); therefore these fluids and tissue filtrates are unsuitable for antigen testing.

Histoplasmin Skin Testing

This has been used in the past and is not useful in endemic areas and in patients with disseminated disease. After intradermal injection of histoplasmin antigen (0.1 mL) prepared from mycelial phase, an induration of 5 mm that develops after 48 hour is considered positive. The reactivity develops 2–4 weeks after primary infection and indicates adequate cellular immunity.

Molecular Methods

Specific oligonucleotide probes (Gen-Probe) have been developed for use in clinical specimens. PCR used in clinical samples has 0–22% sensitivity and 80–100% specificity.

TREATMENT

Amphotericin B and itraconazole are the drugs of choice. Treatment plans are detailed in **Table 1**.

Table 1 Treatment of histoplasmosis

Manifestation	Treatment
Acute pulmonary histoplasmosis (Severe illness)	Amphotericin B for 2 weeks, followed by itraconazole for 12 weeks
Disseminated histoplasmosis	Amphotericin B for 2 weeks, followed by itraconazole for 6 months
Isolated meningitis	Amphotericin B for 3 months, followed by itraconazole for 12 months
Rheumatological complications and pericarditis	Nonsteroidal anti-inflammatory drugs (NSAIDs) for 2–12 weeks

Dosage: Amphotericin B—1 mg/kg daily; Itraconazole—5–10 mg/kg in two divided doses.

PROGNOSIS

Histoplasmosis is self-limited in majority of the healthy individuals. In extremes of age and immunocompromised people serious illness occurs. The cure rate is high for children who receive appropriate therapy for serious acute illness. Data to predict the occurrence of long-term complications is currently unavailable.

PREVENTION

Individuals with impaired CMI who reside in or travel to endemic areas must be educated about activities that may result in inhalation of aerosolized spores. If unavoidable, use of NIOSH (National Institute for Occupational Safety and Health) certified mask is recommended. When potentially contaminated sites are being manipulated, the aerosol formation may be reduced by prior dampening of the areas with water. Prophylactic itraconazole may be given to HIV infected persons with exposure to bird droppings.

IN A NUTSHELL

1. Histoplasmosis is an under-recognized entity in India.
2. Histoplasmosis is an AIDS defining condition.
3. Histoplasmosis manifestations are seen primarily in immunocompromised children only.
4. Histoplasmosis should be considered in the differential diagnosis of prolonged fever, oral ulcers and adrenal enlargement.
5. Histoplasmosis should be considered as differential diagnosis in TB patients with granulomatous disease who do not respond to antituberculous treatment (ATT).
6. Antifungal therapy leads to excellent outcome in most patients.

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Chapter 33.9

Pneumocystis Jirovecii (previously classified as *P. Carinii*)

Ira Shah, Khushnuma Mullanfiroze

Pneumocystis jirovecii (*P. carinii*) is a ubiquitous parasite and opportunistic resident of the human bronchoalveolar lumen and a variety of other mammalian species. It has some common features of protozoa, but molecular studies have shown greater genetic homology to fungi. *Pneumocystis* organisms are host specific, with those infecting humans designated *P. jirovecii*. This microorganism replicates under immunosuppressive conditions, ultimately resulting in interstitial pneumonia called *Pneumocystis* pneumonia (PCP), which is generally lethal if left untreated. The infection remains localized to the lungs.

Information on prevalence of *Pneumocystis* pneumonia (PCP) in immunocompromised children with pneumonia in Southeast Asia is limited. Most children are believed to have been exposed to the organism by age 3 or 4 years and its occurrence is worldwide.

PATHOPHYSIOLOGY

The 5–7 mm cyst contains up to eight pleomorphic intracystic bodies (sporozoites). Once excysted, sporozoites become trophic forms (trophozoites). Once inhaled, all these forms reside in the alveoli of the lung. The trophic form of *Pneumocystis* organisms attach to the alveoli. Multiple host immune factors, importantly, CD4+ T-cells and macrophages, hinder uncontrolled replication of *Pneumocystis* organisms and subsequent development of illness, in immunocompetent hosts. Therefore in immunocompromised hosts, when activated alveolar macrophages and CD4+ T-cells are unable to eradicate *Pneumocystis* organisms, pneumonia and other manifestations of the disease ensue. Lung injury is directly related to the *P. jirovecii*-specific inflammatory response rather than to the organism burden per se. Thus, there seems to be a role of steroids to control the inflammation and hypoxia in these patients.

Children with primary immune deficiencies, e.g., hypogammaglobulinemia, severe combined immunodeficiency (SCID); HIV infection with low CD4+ T levels; malignancies and those on immunosuppressive therapy are at increased risk of acquiring PCP.

CLINICAL FEATURES

Pneumocystis pneumonia presents with nonspecific respiratory symptoms, including tachypnea and cough. Two somewhat different clinical patterns have been observed.

The endemic infantile form of PCP, originally described in outbreaks in European nursing homes for infants, is an interstitial plasma cell pneumonitis. A bronchiolitis-like illness can occur, with prominent tachypnea and dyspnea in the absence of fever. Intercostal retractions are marked, and as the course progresses, flaring of the nasal alae and cyanosis can be observed, and crackles are heard bilaterally. There may be nonspecific symptoms like anorexia, diarrhea, vomiting and listlessness. The untreated course is prolonged over many days to a few weeks, and at least half of these patients die.

Pneumocystis pneumonia in older children and adults begins abruptly with fever, tachypnea, and cough. Intercostal retractions and flaring of the nasal alae may occur, but breath sounds are normal and rales are not heard. The untreated course is progressive, and all untreated patients die within a month. An occasional older child may have complains of substernal pain.

Pneumocystis pneumonia needs to be differentiated from acute respiratory distress syndrome, cytomegalovirus pneumonitis, lymphocytic interstitial pneumonia (LIP), mycoplasma infections, legionellosis, tuberculosis, and *Mycobacterium avium* complex (MAC) infection.

APPROACH TO DIAGNOSIS

Since initial symptoms are nonspecific, always keep a high index of suspicion in those at risk. Suspect PCP in a clinical setting of immunosuppression (primary or secondary) with signs of respiratory distress and hypoxemia. Chest X-ray shows bilateral diffuse reticulogranular infiltrates (**Fig. 1**). *Pneumocystis* is identified either by staining methods which include Grocott-Gomori silver stain, toluidine blue, polychrome stains, fluorescein-labeled monoclonal antibody stains on specimens such as bronchoalveolar lavage (BAL), tracheal aspirate, transbronchial lung biopsy, bronchial brushings, percutaneous transthoracic needle aspiration or open lung biopsy. PCR analysis of the specimen offers a rapid diagnostic method but is not yet standardized for clinical use. Though hypertonic saline-induced sputum samples may be used, absence of organism in induced sputum samples cannot exclude the infection. Open lung biopsy though most reliable is unacceptable clinically and BAL is the most practical method for acquiring the respiratory sample. Endotracheal tube aspirates for those on mechanical ventilation may also be used for diagnosis.

Some studies have stated the role of estimating serum lactate dehydrogenase (LDH) levels in diagnosis and monitoring treatment of patients with PCP pneumonia. Patients with PCP and an initial markedly elevated serum LDH level or a rising serum LDH level despite PCP treatment have a worse prognosis and decreased survival rate, in some studies.

P. jirovecii persists in the lungs for many days after the onset of specific therapy. Under certain circumstances, such as children with terminal stages of untreatable cancer and patients with uncontrollable bleeding disorders, where diagnostic procedure may not be possible, therapy can be initiated immediately and the procedure performed later.

Severity of PCP grading is based on severity of hypoxia, classified using alveolar-arterial (A-a) gradient as follows: < 35 mm Hg—mild; 35–45 mm Hg—moderate; > 45 mm Hg—severe. Severe disease is also indicated by a room air partial pressure of oxygen PaO₂ lower than 70 mm Hg.



Figure 1 Chest X-ray showing *Pneumocystis* pneumonia (PCP) with basal and perihilar haziness

MANAGEMENT

Supportive Care

As dictated by the clinical condition, supportive care must aim to achieve adequate oxygenation and hydration. 5–10% of AIDS patients might require mechanical ventilation whereas 50–60% of patients without AIDS require ventilation.

Specific Therapy

While officially classified as a fungal pneumonia, PCP does not respond to antifungal treatment, though some reports state successful use of echinocandins recently. Currently, antibiotics are recommended for treatment of mild, moderate and severe PCP. Intravenous or oral trimethoprim-sulfamethoxazole [(TMP-SMX) 15–20 mg/kg/day of TMP and 75–100 mg/kg/day of SMX in four divided doses] has been shown to be as effective as intravenous pentamidine and more effective than other alternative treatment regimens. The parenteral route may be considered in those with serious illness or in those with gastrointestinal side effects. Duration of treatment is 3 weeks for HIV infected children and 2 weeks for other patients. Adverse effects of TMP-SMX are erythema multiforme, Stevens-Johnson syndrome (SJS), bone marrow suppression, hepatitis, and interstitial nephritis. For mild rash, TMP/SMX can be temporarily discontinued and restarted when rash resolves. If SJS occurs, therapy should be discontinued and not restarted.

In cases of nonresponse to TMP-SMX within 5–7 days or non-tolerance, IV pentamidine is used. If intravenous access is not available, the drug can be given by deep intramuscular injection, but serious reactions at the injection site, such as soft tissue necrosis and abscess, are common. Other adverse reactions occur in up to 70% of cases and include renal and hepatic dysfunction, thrombocytopenia, anemia, hypotension, abnormally high or low blood glucose concentrations, and rash. Other alternative drugs include atovaquone, trimetrexate glucuronate or combinations of trimethoprim plus dapsone or clindamycin plus primaquine, pyrimethamine-sulfadoxine and aerosolized pentamidine (**Table 1**).

Corticosteroids

Corticosteroids are used as adjunctive initial therapy in patients with a PaO_2 less than 70 mm Hg or an A-a gradient of 35 mm Hg and greater. Methylprednisolone, 2 mg/kg/day, has been used

in children. The dose should be tapered and the corticosteroid discontinued in the recovery stage of pneumonia. The effect of corticosteroid in this setting is probably modulation of the inflammatory response.

PREVENTION

Patients at risk of PCP must receive chemoprophylaxis. In patients with HIV, PCP prophylaxis is recommended in following situations:

- All HIV exposed infants from 4 weeks of age (infants born to HIV infected mothers) till proven to be HIV negative
- All HIV infected asymptomatic infants till 1 year of age
- All symptomatic HIV infected children (WHO stage 2 and above)
- After initial treatment for PCP
- All HIV infected children with CD4 less than 200 cells/cumm in children above 5 years of age and less than 25% in children below 5 years of age irrespective of symptoms.

How Long to give Prophylaxis?

- In HIV exposed infants till proved to be HIV negative
- In patients on ART, if there is evidence of rise in CD4 count of more than 200 cells/cumm in children above 5 years of age and more than 25% in children below 5 years of age on occasions (at least 3 months apart), consider stopping the prophylaxis
- All HIV infected children who do not receive ART and are symptomatic—prophylaxis should be continued indefinitely.

Due to ease of administration, relative lack of toxicity and established role against PCP, TMP-SMX (5 mg/kg TMP and 25 mg/kg SMX PO once or in two divided doses given for consecutive days a week or on alternate days) is the most commonly used drug for primary and secondary prophylaxis in immunocompromised children. For those intolerant to TMP-SMX, aerosolized pentamidine, atovaquone or dapsone may be used. Dapsone orally at a dose of 2 mg/kg/day or 4 mg/kg once weekly can be used. Dapsone is effective in the prevention of PCP, but adverse reactions similar to those caused by sulfonamides can occur. The total dose should not exceed 100 mg/day or 200 mg per dose weekly.

Table 1 Treatment of *Pneumocystis pneumonia* (PCP)

Drugs	Dosing	Remarks
TMP/SMX	15–20 mg/kg of TMP IV/PO in four divided doses for 21 days	Drug of choice. Shift to oral administration as soon as clinical improvement occurs
Primaquine/clindamycin	Primaquine base 0.3 mg/kg OD PO (max 30 mg/day) + Clindamycin 10 mg/kg IV or PO every 6 hour (max: 600 mg IV, 300–450 mg PO) for 21 days	Alternative therapy. Data in children not available
Dapsone/trimethoprim	Dapsone—2 mg/kg/day OD PO + Trimethoprim 15 mg/kg/day in 3 divided doses PO for 21 days	Limited data in children. Alternative therapy
Steroids	Prednisolone Day 1–5—2 mg/kg/day PO BD Day 6–10—1 mg/kg/day PO Day 11–12—0.5 mg/kg/day PO OR IV/IM Dexamethasone 0.3–0.5 mg/kg 6 hourly for 5 days	Indications: $\text{PaO}_2 < 70$ mm of Hg at room air

PROGNOSIS

Without treatment, PCP is universally fatal, within 3–4 weeks of onset. The mortality depends more on the inflammatory response rather than the organism burden. Patients requiring mechanical ventilation have a higher mortality rate. Patients remain at risk for *P. jirovecii* pneumonia as long as the immunosuppression persists and hence continuous prophylaxis is warranted in most patients.

IN A NUTSHELL

1. Suspect *Pneumocystis* pneumonia (PCP) in any immuno-compromised child with fever, cough and tachypnea.
2. Steroids may be required in patients with PCP and hypoxia.
3. Treatment should be initiated even if definite diagnosis cannot be established due to delay in tests.
4. Patients at risk of PCP must receive chemoprophylaxis.

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Section 34 RICKETTSIAL AND OTHER INFECTIONS

Section Editors S Balasubramanian, Piyush Gupta

Chapter 34.1 Epidemiology, Classification, and Approach to Diagnosis of Rickettsial Infections

Narendra Rathi

Rickettsial diseases are unique among all infectious diseases in being one of the most difficult to diagnose and at the same time one of the most easy to treat infections. Difficulty in diagnosis is the result of low index of suspicion, nonspecific signs and symptoms, and absence of widely available sensitive and specific diagnostic tests while ease of treatment is due to rapid defervescence seen with the most inexpensive antibiotics, early in the course of disease. They have been one of the great scourges of mankind, occurring in devastating epidemics during times of war and famine. These infections in the past have taken more lives than all the wars combined together. Rickettsial diseases are some of the most important re-emerging infections of the present times.

EPIDEMIOLOGY

These infections are prevalent throughout the world. Due to low index of suspicion, unavailability of proper diagnostic tests and poor reporting system, reported numbers are always an underestimate in India. Rickettsial disease in India has been documented from Delhi, Jammu and Kashmir, Himachal Pradesh, Uttaranchal, Rajasthan, Assam, West Bengal, Maharashtra, Kerala, Puducherry, Karnataka and Tamil Nadu.

The family rickettsiaceae comprise a group of microorganisms which occupy a place between bacteria and viruses. Rickettsiae are small, nonflagellate, gram-negative pleomorphic coccobacilli and

obligate intracellular parasites. They are transmitted by arthropod vectors, such as lice, fleas, ticks and mites, in which they are found in the alimentary canal. Rickettsia infects vascular endothelium and reticuloendothelial cells. They need tissue cultures and laboratory animals for their isolation as their growth does not occur on cell free media being obligate intracellular pathogens. Transmission to humans occurs by infected arthropod vector or by exposure to infected animal reservoir host. Poorly maintained kitchen garden and long grass, pets infected with vectors, animal sheds in vicinity of houses are important factors for transmission.

PATHOGENESIS

Vasculitis is the basic pathogenetic mechanism and explains clinical features like skin rash, microvascular leakage, edema, tissue hypoperfusion and end-organ ischemic injury. Formation of thrombi can lead to tissue infarction and hemorrhagic necrosis. Inflammation and vascular leakage leads to interstitial pneumonitis, noncardiogenic pulmonary edema, cerebral edema and meningoencephalitis. Infection of endothelial cells also induce procoagulant activity that promote coagulation factor consumption, platelet adhesion and leukocyte emigration and may result in clinical syndrome similar to disseminated intravascular coagulation.

CLASSIFICATION

Family rickettsiaceae comprises three genera namely *Rickettsia*, *Orientia* and *Ehrlichia*. Former members of this family, *Coxiella burnetii* which causes Q fever and *Rochalimaea quintana* causing trench fever have been excluded because the former is not primarily arthropod-borne and the latter not an obligate intracellular parasite. Various members of *Rickettsia* can be grouped into four biogroups based on the lipopolysaccharide group antigen (Table 1).

Table 1 Classification of rickettsial disease

Biogroup	Disease	Vector	Host	Organism
Spotted fever	Rocky mountain spotted fever (RMSF)	Tick	Dogs, rodents	<i>Rickettsia rickettsii</i>
	Rickettsialpox	Mite	Mice	<i>Rickettsia akari</i>
	Indian tick typhus/Boutonneuse fever/Mediterranean spotted fever (MSF)	Tick	Dogs, rodents	<i>Rickettsia conorii</i>
Typhus	Epidemic louse borne typhus	Louse	Human	<i>Rickettsia prowazekii</i>
	Brill-Zinsser disease (recrudescent typhus)	Louse	Human	<i>Rickettsia prowazekii</i>
	Endemic/Murine flea borne typhus	Flea	Rats	<i>Rickettsia typhi</i>
Scrub typhus	Scrub typhus	Chigger	Rodents	<i>Orientia tsutsugamushi</i>
Miscellaneous	Ehrlichiosis and Anaplasmosis	Tick	Deer, dogs, rodents	<i>Ehrlichia</i> , <i>Anaplasma</i>
	TIBOLA (tick borne lymphadenopathy)	Tick	Wild boar	<i>Rickettsia slovaca</i>
	DEBONEL	Tick	Wild boar	<i>Rickettsia slovaca</i>

Abbreviation: DEBONEL, dermacentor borne necrosis-eschar-lymphadenopathy.

INDIAN SCENARIO

In India, the most common Rickettsial infections are Indian tick typhus and scrub typhus. There are some differences in epidemiological aspects among these biogroups. Arthropods maintain the infection naturally by either transovarial transmission (passage of the organism from infected arthropods to their progeny seen in spotted fever group and scrub typhus) wherein arthropods act as vector as well as reservoir; or without transovarial transmission seen in typhus fever group, wherein arthropods act only as vector. Vector to human transmission occurs as vector defecates while feeding (flea feeding reflex) so that feces contaminate pruritic bite wounds (seen with typhus fever group) or primarily by bite, where regurgitation of infected saliva occurs during feeding (seen with spotted fever group and scrub typhus).

DIAGNOSIS

Rickettsial disease should be kept in mind in all cases of fever with rash, fever without focus, pyrexia of unknown origin, fever with edema, dengue-like illness, meningoencephalitis/aseptic meningitis, and infective vasculitis. An algorithm for diagnosis of rickettsial diseases is given in **Figure 1**. Rathi et al. have suggested Rathi, Goodman, Aghai scoring system to diagnose spotted fever rickettsioses using clinical, laboratory and epidemiological features (**Table 2**). This scoring system with a cutoff score 14 (total score 35) has been reported to have high sensitivity (96.1%) and specificity (98.8%), similar to the detection of specific IgM antibody by ELISA (*Indian Pediatrics*, 2011).

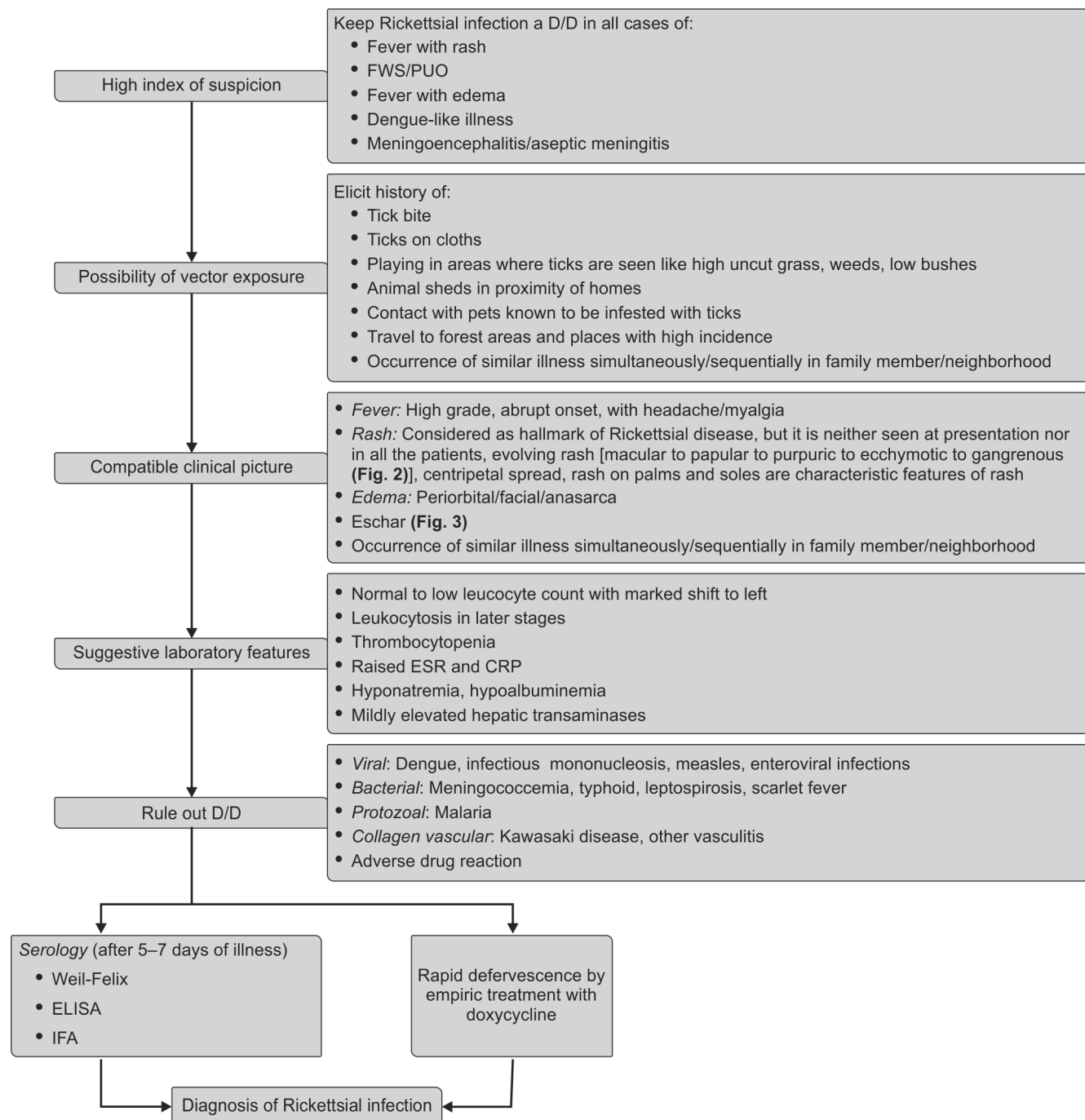


Figure 1 Algorithmic approach to diagnosis of rickettsial infections

Table 2 RGA scoring system to diagnose spotted fever rickettsial infections

<i>Clinical features</i>	<i>Score</i>	<i>Laboratory features</i>	<i>Score</i>
Rural	1	Hemoglobin < 9 g/dL (%)	1
Pets	1	Platelets < 150,000 (cells/L)	1
Tick exposure	2	CRP > 50 mg/dL	2
Tick bite	3	Serum albumin < 3 g/dL	1
Nonexudative conjunctival congestion	2	Urine albumin	1
Maculopapular rash	1	SGPT > 100 U/L	2
Purpura	2	Serum Na < 130	2
Palpable purpura/ecchymosis/necrotic rash (Fig. 2)	3		
Rash appearing 48–96 hours after fever	2		
Pedal edema	2		
Rash on palms and soles	3		
Hepatomegaly	2		
Lymphadenopathy	1		
Total	25		10

**Figure 2** Gangrenous rash

[Reprinted with permission from Rath N and Rath A. *Ped Inf Dis J*. 2013;5(2):64-68]

**Figure 3** Eschar near medial canthus of right eye

[Reprinted with permission from Rath N and Rath A. *Ped Inf Dis J*. 2013;5(2):64-68]

IN A NUTSHELL

1. Rickettsial infections are an important zoonoses emerging and re-emerging with high morbidity and mortality if not recognized and treated promptly.
2. High index of suspicion is needed to diagnose rickettsial diseases in nonspecific febrile illnesses on the basis of clinical, laboratory and epidemiological clues.
3. Vasculitis with capillary leak is the basic pathophysiology, and hence these infections present as dengue-like diseases (e.g., dengue fever, leptospirosis, septicemia, etc.).
4. Fever, rash, edema, eschar, hepatosplenomegaly are usual clinical features; and meningoencephalitis, adult respiratory distress syndrome and disseminated intravascular coagulation are the usual complications.
5. Possibility of vector exposure, compatible laboratory features and ruling out differential diagnosis are key elements for diagnosis. In such cases, empirical treatment with doxycycline leading to rapid defervescence in 48 hours clinches the diagnosis.
6. RGA scoring system has been suggested as an important clinical tool for diagnosis of spotted fever group of rickettsiosis.
7. Serological tests like Weil–Felix, ELISA and IFA are useful only after 5–7 days of illness.

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Chapter 34.2

Spotted Fevers

Atul A Kulkarni

Spotted fevers are caused by *Rickettsia* spp. in the spotted fever group (SFG), and these are recognized for more than a century. In most of these diseases, clinical signs are similar. However, the clinical signs are mild and self-limiting in some patients while in some others, these can be severe and life-threatening. For many years, it was believed that spotted fevers were caused by a handful number of organisms including *R. rickettsii* (Rocky Mountain spotted fever) in the Americas, *R. conorii* in the Mediterranean region, and *R. australis* (Queensland tick typhus) in Australia. In the past three decades, many other species of organisms have been recognized as pathogens in humans.

Based on their serological reactions, the *Rickettsia* species are divided into *spotted fever* and *typhus* groups. The outer membrane protein A (ompA) gene is observed in SFG unlike the typhus group of organisms.

The earliest description of Rocky mountain spotted fever (RMSF) dates as far back as 1873. Howard Taylor Ricketts (1871–1910) studied RMSF in the Bitterroot Valley of Montana. He died eventually of typhus fever in Mexico City. Hence, the genus *Rickettsia* is rightly named after him.

Spotted Fever in India

Megaw first observed spotted fever in India during the year 1917 in the foothills of the Himalayas. Reports of Indian tick typhus (ITT) fever have come from all over the country. Recent reports state that ITT is prevalent in many districts of Maharashtra, Karnataka, Tamil Nadu, Andhra Pradesh and Kerala. ITT is endemic in the rural part of these areas.

ETIOLOGY

Rickettsia spp. are the causative organisms of spotted fevers. These are Gram negative coccobacilli belonging to the family rickettsiaceae and order rickettsiales of alpha-proteobacteria. SFG of *Rickettsia* contains many human pathogens that are transmitted by tick bites. Approximately 25 different types of spotted fevers have been reported.

Rocky mountain spotted fever is caused by *R. rickettsii*. In Brazil, this fever is called as Brazillian spotted fever. Mediterranean spotted fever (MSF) which is also called as boutonneuse fever is caused by *R. conorii* subsp. *conorii*. Other subspecies of *R. conorii* cause Israeli spotted fever (*R. conorii* subsp. *israelensis*), Astrakhan spotted fever (*R. conorii* subsp. *caspia*) and Indian tick typhus (ITT) (*R. conorii* subsp. *indica*). *R. slovaca* and *R. raoultii* are the causative organisms for the illness called TIBOLA (tick-borne lymphadenopathy) and DEBONEL (Dermacentor-borne necrosis erythema lymphadenopathy). African tick-bite fever (*R. africae*), Japanese or Oriental spotted fever (*R. japonica*), Queensland tick typhus (*R. australis*) and Flinders island spotted fever (*R. honei*) are some of the other named spotted fevers. Some of the pathogenic members of the SFG rickettsiae are transmitted by other arthropods. *R. felis* causes a syndrome called as flea-borne spotted fever or cat-flea typhus. Rickettsialpox is caused by *R. akari* and it is transmitted by mites.

TRANSMISSION

Tick-Borne Spotted Fevers

Most of the SFG rickettsiae have ticks as their vectors (Fig. 1). These sustain the infection through transovarial route, i.e., the organisms



Figure 1 An adult female *Rhipicephalus sanguineus* (brown dog tick)
Source: Public health image library (PHIL), CDC, USA.

are transmitted from the infected ticks to their progeny. Transstadial passage of organisms is also described. The ticks inject organisms into their mammalian hosts that include the humans, by regurgitating the infected saliva while feeding. Dogs and rodents serve as reservoir hosts for these vectors. These reservoir vectors can themselves develop the disease and are important vehicles for bringing potentially infected vectors into environment shared by humans. At times, crushed tick's tissues, fluids or feces enter the human body through breaks in the skin—resulting in entry of the rickettsial organisms. Blood transfusion is yet another route through which these organisms can be transmitted from an infected person to the noninfected.

Flea-Born and Mite-Born Spotted Fevers

R. felis and *R. akari* are the SFG rickettsiae that is transmitted by arthropods other than ticks. *R. felis* is predominantly found in cat flea, *Ctenocephalides felis*, which is at present the only arthropod known to be a biological vector. *R. akari* is transmitted by mite.

PATHOPHYSIOLOGY

There are two ways through which the rickettsial organisms are inoculated into the dermis of the skin: one of these is through a direct bite from the tick and another one is when the feces of the infected fleas come in contact with the damaged skin of the victim. Once inside the blood stream, these bacteria infect the endothelium. Attachment to the host cell is thought to be the first step of rickettsial pathogenesis. The outer membrane proteins are thought to be the primary adhesins. The host cells consume the rickettsiae that are attached to their cell membrane through phagocytosis. Since the rickettsial organisms enter the cells that do not normally phagocytose the outer particle, it is postulated that these organisms have the ability to induce the process of phagocytosis in the host cells. Once inside the cell, it is observed that the rickettsiae quickly enter the cytoplasm after lysing the phagosome membrane. The rickettsial organisms of SFG rarely accumulate in large numbers within the host cells, and these do not cause their lysis. These stimulate polymerization of the actin tails derived from the host cell in order to escape. These polymerized actin tails propel them through cytoplasm and into the tips of membranous extrusions from which they emerge. Signs of cell membrane damage associated with influx of water are observed within the infected cells. Rickettsiae are known to proliferate on the endothelium of smaller blood vessels where they release cytokines leading to disintegration of the endothelium. It leads to fluid

leakage and platelet aggregation. Focal proliferation of monocytes and polymorphs leads to occlusive end-arteritis or microvasculitis. It results in micro-infarctions and *Typhus nodules of Wohlbach* that are typical of typhus fevers. This mode of cell injury and its sequelae are typically observed in brain, heart muscle, skeletal muscle, skin, liver, lungs and kidneys. Occlusion of the venous leading to gangrene of the extremities is also observed.

CLINICAL MANIFESTATIONS

In children incubation period varies from 2 days to 14 days with a mean of 7 days. However, it may extend up to 28 days. Quite often, history of exposure to tick bite or close contact with an infected pet is forthcoming. Many times, history of travel from an endemic spot and similar illness in family members is available. Severity of manifestations varies from a mild, self-limiting illness to a life-threatening disaster.

Initially, the illness appears to be nonspecific and patients present with fever, headache, anorexia, restlessness and muscle pains. Pain and tenderness in calf region is common in children. Nausea, vomiting and diarrhea are the common gastrointestinal symptoms. Abdominal pain is a frequent complaint earlier in disease. Skin rash is usually not present till the disease has progressed for 2–4 days. In as many as 44% of the patients, the typical triad of fever, headache and rash is observed. Core body temperature can exceed 40°C, and it can either remain elevated or fluctuate drastically. A severe and unremitting type of headache, often not responding to analgesics, is common. Rash is usually discrete to begin with blanching macules or maculopapular rashes which can be pale or rose-red are typically seen on the extremities like ankles, wrist, and lower limbs.

Later, rash spreads quickly to involve the entire body including palms and soles (**Fig. 2**). Rash becomes more petechial or hemorrhagic, sometimes with palpable purpura (**Fig. 3**) after several days. The petechiae may enlarge to become ecchymosis and necrotic (**Fig. 4**) in severe form of the disease. Even though severe vaso-occlusive disease secondary to rickettsial vasculitis and vessel thrombosis is rare, when it does take place, it can result in gangrene of the digits (**Fig. 4**), toes, earlobes (**Fig. 5**), and entire limbs. *Tache noire* refers to painless eschar which may be observed at the initial site of tick attachment, and it may be associated with regional lymphadenopathy. Edema over the dorsum of hand or foot, periorbital edema and generalized edema are sometimes seen and so are hepatosplenomegaly and generalized lymphadenopathy.

Neurological Involvement

The name typhus originated from the Greek word *typhos*, which means smoky and refers to the cloudy sensorium of patients with typhus and other life-threatening rickettsioses. Rickettsial



Figure 3 Palpable purpura over lower limbs



Figure 4 Necrotic rash with gangrene of digits



Figure 2 Petechial rash over palm



Figure 5 Gangrene on earlobe

encephalitis manifests first as confusion or lethargy, as the disease progresses, stupor or delirium, ataxia, coma, deafness and seizures are observed. Involvement of blood vessels contiguous to the cerebrospinal fluid leads to pleocytosis in one-third of patients, usually 10–100 cells/mm³ with predominance of lymphocytes and macrophages. However, occasionally, more than 100 cells/mm³ with polymorphonuclear predominance are observed. Coma or seizures may be associated with fatal outcome.

Pulmonary Involvement

The pulmonary microcirculation is heavily infected by *Rickettsia* in severely ill patients. The effect is ARDS. Interstitial pneumonitis and alveolar edema are the most severe manifestations.

Renal

At times, rickettsial disease presents as renal failure indicating adverse prognosis. Sometimes disseminated intravascular coagulation like syndrome, myocarditis, gangrene and hepatic failure are seen in spotted fever.

INDIAN TICK TYPHUS (*RICKETTSIA CONORII* SUBSP. *INDICA*)

Until Megaw put forth the view that tick typhus exists in India as a distinct entity, ITT used to be diagnosed as Rocky mountain spotted fever (RMSF) because of the similarity of clinical illness.

R. conorii, the bacterium was considered to be the cause of ITT. Subsequent serologic studies showed significant differences in antibody responses of patients of ITT with the ITT rickettsial and type strains of *R. conorii*. Recently, using molecular methods, it was demonstrated that these rickettsiae are closely related although differing, as reflected in antigenic variation. Zhu et al. have proposed recently that the causative agent of ITT is a subspecies of *R. conorii*, and it is different from the agent of MFS, designated *R. conorii* subsp. *indica*.

Indian tick typhus has various names in the local language: *Kan Kapaya disease* (gangrene of earlobe), *Motha Govar*, *Ghodya Govar* and *Bibtya*. ITT is prevalent in many districts of Maharashtra, Karnataka and Tamil Nadu. The tick is the reservoir of infection. Various tick genera (e.g., *Rhipicephalus*, *Ixodes*, *Boophilus*, *Haemaphysalis*) have been incriminated as vectors. Rickettsial organisms can also be transmitted to dogs, rodents and other animals which assist in maintaining the disease cycle, and these animals bring these dangerous pathogens near human beings. Clinical presentation of ITT is similar to that of RMSF with less severity. But recent Indian reports state that ITT has clinical features as severe as those of RMSF.

The rash in ITT is frequently purpuric and inoculation eschar at the bite site is unusual unlike RMSF. A nonpruritic macular rash is commonly seen initially on the wrist, forearms, ankles or scrotum. It can appear from the 2nd to 4th day. It quickly spreads to involve the palms or soles along with trunk and extremities. To begin with, the spot blanch when pressed, but later develop typical petechiae.

DIAGNOSIS

At present, an assay providing rapid confirmation of early rickettsial fever is not widely available. The decision to treat must be based on epidemiological and clinical data. It is not advisable to wait for confirmation by laboratory results.

Hematology

During early course of disease, the total leukocyte count can either be normal or below normal with marked shift to left. Leukocytosis is seen in 30% of the cases as the disease progresses. In about 60% of the cases, platelet counts are low.

Biochemistry

Hyponatremia and reduced albumin levels in the blood reflect increase in vascular permeability. Often, hepatic transaminase levels are increased.

Serology

Many serological tests are available for diagnosing rickettsial diseases. Microimmunofluorescence, immunoperoxidase assay, indirect hemagglutination, enzyme-linked immunosorbent assay, latex agglutination, dot blot immunoassay (including dip-stick test) and Weil-Felix (WF) test are some of these. Since these tests become positive 5–7 days after the onset of symptoms, they cannot be depended upon to initiate suitable therapy.

Weil-Felix Test

This is a heterophile antibody test which has the sharing of antigens between *Rickettsia* and *Proteus* as its basis. It shows agglutinins to *Proteus vulgaris* strain OX 19, OX 2, OX K. Most of the literature published in western world has discouraged using this test for diagnosing rickettsial infections. Even though poor sensitivity of WF test is well-documented, a good correlation is observed between the results of WF test and detection of IgM antibodies by an indirect immunofluorescence assay (IFA). WF test can at best be used as a screening test because it detects more cases than misdiagnosed ones and also when it is positive, it is reasonably specific. In spite of the drawbacks, WF test still serves as a useful and affordable diagnostic tool for laboratory diagnosis of rickettsial disease—especially in the resource-starved developing world. Chief criteria for diagnosis by WF test are either a fourfold rise in titer in paired sera or a single titer of more than 1:320. Dependence on WF test is accepted in those circumstances where definitive investigations are not available. However, like any other test, WF test must be interpreted in appropriate clinical context.

Immunofluorescence Assay

This test is regarded as the gold standard test for serodiagnosis of rickettsial disease and allows detection of IgG and IgM antibodies. IgM titer more than 1:640 suggests acute infection. IgM begins to appear at 5–10 days and peak levels are reached 3–4 weeks after the onset of symptoms. IgG levels of more than 1:254 indicate acute infection. IgG greater than 1:64 but less than or equal to 1:125 suggest previous infection. Chief drawbacks of IFA are that it is expensive and not widely available.

Enzyme-linked Immunosorbent Assay

This test was initially introduced for detection of antibodies against *R. prowazekii* and *R. typhi*. This test is not only highly sensitive but also reproducible, allowing the differentiation of IgM and IgG antibodies. This technique was also adapted to diagnose RMSF and scrub typhus.

PCR-based Detection

Detection of *Rickettsia* from tissues and blood of infected patients is the technique of choice for early diagnosis (within first week) before seroconversion.

Amplification of specific DNA by PCR provides a quick method for detecting rickettsial infections. Real-time PCR might offer additional advantages of speed, reproducibility and low risk for contamination. Western immunoblot assay can also be used for early diagnosis.

DIFFERENTIAL DIAGNOSIS

Spotted fevers can mimic meningococcemia, measles and enteroviral exanthemas. Typhoid fever, leptospiral infection,

parvoviral infection, scarlet fever, rubella, Kawasaki disease, toxic shock syndrome, thrombotic thrombocytopenia purpura (TTP), hemolytic uremic syndrome, Henoch-Schönlein purpura, acute abdomen, aseptic meningitis, hepatitis, dengue fever, infectious mononucleosis, drug reactions, malaria, tularemia, anthrax and other causes of pyrexia of unknown origin are also included in differential diagnosis.

TREATMENT

Prompt initiation of therapy with appropriate antibiotics prevents more severe form of disease and avoids mortality. Usually, treatment for spotted fevers is initiated without waiting for laboratory confirmation. Even though treatment is not always necessary for some spotted fevers (e.g., rickettsialpox), antibiotics may be administered to shorten the illness. Tetracycline and chloramphenicol are two time-tested drugs to effectively treat rickettsial infections in patients of all ages including children with spotted fevers. Doxycycline is the drug of choice in all age groups. Tetracycline and doxycycline may cause discoloration of teeth in children who are less than 8 years of age while chloramphenicol can rarely cause aplastic anemia. Doxycycline can be used safely in young children because tooth discoloration is dose dependent and children are unlikely to require multiple courses.

Recommended Treatment Regimens

- *Doxycycline*: 2.2 mg/kg BID PO or IV, maximum 200 mg/day.
- *Tetracycline*: 25–50 mg/kg/dose 6 hourly PO, maximum 2 g/day.
- *Chloramphenicol*: 50–100 mg/kg/day 6 hourly, maximum 3 g/day.

The therapy should be continued for a minimum of 5–7 days and for at least 3 days until the patient is afebrile in order to avoid relapse. It is observed that patients treated with these regimens tend to become afebrile within 48 hours. Thus a typical treatment regimen lasts for less than 10 days.

Supportive Care

Appropriate antimicrobial therapy will resolve most infections rapidly and do not require hospitalization or other supportive care. Occasionally, intensive care treatment is required for severely infected children. A special attention to hemodynamic status is necessary in severely sick children because iatrogenic pulmonary edema or cerebral edema frequently occurs due to diffuse microvascular injury to the lungs, meninges and brain. Prudent use of corticosteroids for meningoencephalitis has been advocated by some, even though no controlled trials have been conducted.

PREVENTION

No vaccines are available. Known tick infested areas should be avoided. Daily inspection of body for tick bites is particularly important. Disinfection of dogs will minimize the tick population. Health education of people about mode of transmission by ticks and means of personal protection is equally important. Prophylactic antibacterial therapy is not recommended because tetracycline and chloramphenicol are only rickettsiostatic. Such therapy not only delays the onset of illness but also results in confusing clinical

picture by prolonging the incubation period. Flea control on pets goes a long way in reducing the risk of flea-borne spotted fever.

PROGNOSIS

Delay in diagnosis and appropriate treatment are the chief factors influencing the severity of illness or death. The case fatality rate was 10% for children and 30% for adults before the advent of effective antimicrobial therapy. A delay in initiating therapy can lead to irreversible vascular or end-organ damage leading eventually to death.

IN A NUTSHELL

1. Except Antarctica, spotted fever disease is prevalent throughout the world, and it is named after different geographic areas. In India, it is known as Indian tick typhus.
2. Majority of spotted fevers are transmitted by ticks. Microvasculitis is the hallmark of rickettsial infection.
3. Patients coming from endemic area and with history of contact with pets like dogs and tick bite should be suspected to have rickettsial infection.
4. Classical triad of symptoms consists of fever, rash and headache (irritability in young children).
5. Clinical features include fever, rash extending over palms and soles, palpable purpura, necrotic rash, gangrene, eschar, lymphadenopathy, edema over the body, pain in the legs and hepatosplenomegaly.
6. Meningoencephalitis, interstitial pneumonitis, ARDS, acute renal failure, myocarditis and disseminated intravascular coagulation are some of the complications.
7. Till date, an assay providing rapid confirmation of early rickettsial disease is not widely available. Immunofluorescence assay (IFA) remains the gold standard test for serodiagnosis of rickettsial disease after 1 week.
8. The decision to treat must be based on epidemiological and clinical data. A delay in treatment while waiting for confirmation of laboratory results must be avoided.
9. Doxycycline and chloramphenicol are the two time-tested drugs recommended to effectively treat rickettsial infections of all ages including children.
10. No vaccines are available. Health education of people about mode of transmission by ticks and means of personal protection is equally important.

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Chapter 34.3

Scrub Typhus

Veena R Parmar

Scrub typhus is a form of rickettsial disease caused by genera *Orientia*. It differs from *Rickettsia* as its cell wall is deficient in lipopolysaccharide, and it exhibits antigenic heterogeneity. Rodents and arthropods are the natural hosts and humans get infected through the vector.

EPIDEMIOLOGY

Scrub typhus is endemic in India, Nepal, China, Tibet, Pakistan, Sri Lanka, Russia, Afghanistan, Japan, South Korea, Indonesia and Taiwan, and Northern Australia. These geographical areas form the famous Tsutsugamushi triangle. In these endemic regions, at any given time around 3% of population might be infected. Recently epidemics of scrub typhus have been reported from northern, eastern and coastal regions of India.

Mainly adults who live or camp in the scrub vegetation areas are susceptible to infection, but any age and sex including children can be affected. Recurrent infections are known as the post infection immunity wanes off in 1–3 years.

ETIOLOGY

Scrub typhus is caused by the intracellular parasite *Orientia tsutsugamushi* a gram-negative proteobacterium of family Rickettsiaceae. It is no more included in genus *Rickettsia* but is classified in genus *Orientia*. The trombiculid mites are the natural hosts. Humans get infection through the bite by the infected larval stage of the trombiculid mite called chiggers. The infection is most common in rainy season from June through November as the mites lay eggs in this season. The trombiculid larvae act as vector as well as reservoir of infection via transovarial transmission to their progeny.

PATHOGENESIS

A papule appears at the site of bite, which later gets necrotic and forms an eschar. Regional lymphadenopathy develops and may be tender. *Orientia tsutsugamushi* invades and replicate within the human monocyte macrophages and endothelial cells and induce expression of a large number of genes such as: type I interferon, interferon-stimulated genes, inflammation-associated genes and apoptosis-related genes and release of inflammatory cytokines like tumor necrosis factor and interleukin-1 β are released. Perivasculitis of small blood vessels sets in. Subsequent to these changes, the local and systemic inflammation sets in thus resulting in multiorgan involvement and clinical presentation.

CLINICAL FEATURES

In children, the disease may vary from being mild to a severe form. A painless eschar develops at the site of bite in about 50% of primary and 30% of secondary infections. Although eschar is found commonly on the lower limbs, other body parts such as arms, neck and scrotal region can be affected especially in children. By the time fever starts, the eschar is fully developed.

The incubation period ranges from 6 days to 20 days and usually corresponds to the eschar stage. There after the constitutional symptoms like headache, anorexia, malaise and abrupt onset of fever (40–40.5°) with chills start. Nearly 40% have pain abdomen, and vomiting. A transient centripetal maculopapular rash appears

on the 5th to 8th day of fever in about 40% cases. Acute loss of hearing, pathognomonic of scrub typhus occurs in a few cases. Regional and generalized lymphadenopathy is found in 20–90% cases and hepatosplenomegaly in about half of the cases. Some patients may develop encephalitis, encephalomyelitis, neurological deficits, myocarditis, disseminated intravascular coagulation, acute kidney injury (AKI), atypical pneumonia and acute adult respiratory distress syndrome like picture in the severe form of disease. The complication rate is less in children but higher in patients above 60 years of age, especially in those with leukocytosis above 10,000/ μ L, or eschar. The symptoms resolve within 36–48 hours with specific and supportive treatment but may last for 2 weeks if left untreated. High levels of Interleukin-8 are associated with a higher disease severity and mortality.

DIAGNOSIS

Scrub typhus should be suspected and excluded in all patients presenting with high-grade fever, rash, lymphadenopathy and renal failure. Presence of eschar and acute hearing loss is pathognomonic. History of visit to endemic areas should be elicited. The diagnosis can be confirmed with serological and other tests as follows. Presence of a combination of leukocytosis, transaminitis and thrombocytopenia in a febrile child with or without eschar coming from an endemic area should alert one to the diagnosis.

The Weil–Felix agglutination test, though not very sensitive and specific but cost effective is still being used. It becomes positive after 5th to 10th day of onset of illness in about 50–70% cases. A fourfold or higher rise in titer to *proteus* OX-K and no reaction to *proteus* OX-2 or OX-19 or a single titer greater than or equal to 1:160 is diagnostic.

Enzyme-linked immunosorbent assay (ELISA); the 56-kDa protein is located on the outer membrane of *O. tsutsugamushi* is highly reactive with patient sera; the trivalent ELISA using whole cell antigen and r56 from the Karp, Kato, and Gilliam strains of *O. tsutsugamushi* (KpKtGm-wc ELISA and KpKtGm r56) is highly sensitive and specific but expensive.

Indirect fluorescent assay is a more sensitive and gold standard test for scrub typhus but is costly. A fourfold rise in antibodies in paired sera is diagnostic. Specific IgM antibodies can also be demonstrated with the indirect immunochromatographic test, which is rapid and highly sensitive and specific.

Polymerase chain reaction (PCR) is a very sensitive test for the detection of *O. tsutsugamushi*. Apart from blood, it can also be performed on the tissue from eschar. The organisms can be detected within 1–3 days of onset of fever by nested PCR which is 100 times more sensitive but expensive than single PCR. *O. tsutsugamushi* can be isolated and cultured from a patient's blood by inoculating it intraperitoneal, into white mice or Guinea pig but is still carried out only in research laboratories.

Early lymphopenia with late lymphocytosis, a decrease in the CD4:CD8 lymphocyte ratio and thrombocytopenia is seen in 75–95% of patients. Transaminase levels may be raised and hypoalbuminemia occurs in about 50% of cases, more so in children. Hyperbilirubinemia is rare. X-ray of chest shows pneumonitis, especially in the lower lung fields. Histologically, focal or disseminated vasculitis and the perivascular infiltration of leukocytes can be seen.

TREATMENT

To reduce the morbidity and mortality, specific and supportive treatment must be initiated early in the course of the disease on the basis of a presumptive diagnosis. Scrub typhus patients respond more promptly and fever resolves within 24–36 hours. Relapses

Table 1 Drug treatment of scrub typhus

Drug	Route and dosage	Duration
Doxycycline or	4 mg/kg/day PO/IV divided q 12 hours x 1 day <i>Maintenance:</i> 2.2–4.4 mg/kg/day IV/PO divided BID for 5–7 days or 3 days after fever subsides (whichever is longer)	5–7 days or afebrile for > 3 days
Tetracycline	25–50 mg/kg/day, maximum 2 g/day PO in 6 hourly divided dosages	
Chloramphenicol	50–100 mg/kg/day IV divided every 6 hours, maximum 4 g/day	5–7 days or afebrile for > 3 days
Azithromycin*	≥ 6 months: 10 mg/maximum 200 mg/day/kg PO on day 1, followed by 5 mg/kg PO on days 2–5	5 days
Rifampicin*	10–20 mg/kg/day IV/PO or 10–20 mg/kg PO twice weekly (DOT); not to exceed 600 mg/day	

*More effective in doxycycline resistant cases. (Reported recently from Thailand)

may occur if the antibiotics are not taken for a long enough period. Drug therapy is shown in **Table 1**.

Supportive measures such as maintenance of fluid and electrolyte balance, prompt and aggressive treatment of shock, maintenance of nutrition, respiratory support, etc. should be provided as per need.

PROGNOSIS

Patients develop serious complications and may even die if treatment is delayed. Mortality ranges from 1% to 60%, depending on the geographic area and the pathogenic strain. Death can occur either from the primary infection or from secondary complications (e.g., pneumonitis, encephalitis, or circulatory failure, acute renal failure, etc.). Most fatalities occur by the end of the second week of infection.

PREVENTION

Achieve adequate vector control by use of insecticides and clearing of scrub vegetation from the camping sites. Bites by chiggers can be minimized by wearing protective clothes and using insect repellents. No effective vaccine against scrub typhus is available currently.

Chemoprophylaxis Doxycycline and chloramphenicol have been tried with variable results. A single dose of doxycycline is given weekly; start before exposure and continue for 6 weeks after exposure. Or a single dose of chloramphenicol or tetracycline given orally once every 5 days for a total of 35 days.

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IN A NUTSHELL

1. Scrub typhus is endemic to India and children also can be affected.
2. Scrub typhus is caused by rickettsia *tsutsugamushi* species of genera *Orientia*. The infection occurs through the bite of infected larval stage of the trombiculid mite called chiggers.
3. Clinically the disease presents as acute febrile illness with lymphadenopathy, rash and other systemic features in more severe forms, particularly acute renal failure. Eschar at the site of bite is pathognomonic.
4. High suspicion index for the disease is helpful in early diagnosis and treatment.
5. Diagnosis can be confirmed by immunological tests.
6. Tetracyclines (doxycyclines) are the drug of choice.
7. Adequate vector control is helpful in prevention.

Chapter 34.4

Epidemic Typhus

Sunil Vaidya, Atul A Kulkarni

Epidemic typhus is a lethal exanthematous disease caused by *Rickettsia prowazekii* and is transmitted by the human louse. Typhus was also known as *Jail Fever*, as it was common in prisons. At present, epidemic typhus is considered as a potential bioterrorism agent (category B, CDC). It may be a serious threat in disaster struck areas of the world, where unhealthy living conditions and social disturbances prevail and the population is prone for louse infestations.

HISTORICAL ASPECTS

The first historical evidence of typhus comes from an outbreak in a Sicily Monastery in 11th century. It then spread throughout the entire Europe in 16th–19th century. These epidemics were described in many wars including the English Civil War (1642–1651), the Thirty Years' War (1618–1648), the Napoleon Wars (1803–1815). During 1618–1648, different kinds of pests related illness, mainly typhus surged in Germany and surrounding nations. In the famous retreat from Russia by Napoleon, more French soldiers died due to typhus than they were killed in war. Typhus epidemics reached the peak in Russia in 1922, when an enormous number of 25–30 million cases and 3 million deaths were reported.

In the year 1928, Charles Nicolle won the Nobel Prize in Medicine for identifying louse as the transmitter of epidemic typhus. In 1948, Paul Hermann Müller, discovered DDT as a highly efficient contact poison against the lice and several arthropods, and was awarded the Nobel Prize for his revolutionary research.

Typhus spread through Europe, North Africa, and the Pacific Islands in the 20th century. As reported by Byrne, by the end of war typhus accounted for more than 10% deaths of the total German population and the disease lead to 90% of deaths in Europe.

TRANSMISSION

Rickettsia prowazekii is the causative organism for epidemic typhus and is carried by body lice. During the feed of lice on a human body, they also defecate. On the scratch of the bite, the feces containing the organisms are inoculated into the wound. Body lice are commonly seen in people who live under cold, overcrowded, dirty conditions, without any opportunities to wash themselves or their clothing.

The reactivation of an earlier infection with epidemic typhus leads to a relatively mild illness and is termed as Brill–Zinsser disease. It affects people years after they have completely recovered from epidemic typhus. The bacteria are reactivated as a result of weakening of immune system, as it occurs in old age, surgery, major illness, etc.

EPIDEMIOLOGY

Epidemic typhus is commonly seen in communities affected by poverty, war, natural calamities like flood, earthquakes and in populations like prisoners, refugee camps, where body lice are easily transmitted and prevalent. Outbreaks are often reported during cold climate as infested clothing is not laundered. Visitors are at risk for epidemic typhus who work with or visit such infested areas.

In India, the reported numbers may be quite less due to non-availability of confirmatory laboratory tests, failure to diagnose

the disease, lack of reporting and inadequate records. However, rickettsial disease in India has been reported in sub-Himalayan populations from Jammu and Kashmir, Himachal Pradesh, also from Uttaranchal and West Bengal.

CLINICAL FEATURES

Many children with fever and maculopapular rash in routine practice are often labeled as viral fever or viral exanthematous fever. With high index of suspicion, typhus or rickettsial infection can be diagnosed earlier. Rickettsioses are difficult to diagnose specifically to their subtypes. The clinical presentations vary with each patient and causative rickettsial subtypes. Within 1–2 weeks of infection, common symptoms like fever, headache, weakness, and muscle aches develop. Maculopapular rash may be present in 10–30% of the patients. The rash starts on the back, chest and abdomen, further spreads to the arms and legs.

Epidemic typhus manifest one or more abnormalities of function of the CNS, such as signs of meningeal irritation or signs of focal or generalized neurological involvement like seizures, hearing loss, confusion, drowsiness and coma. Myocarditis, pulmonary involvement (interstitial pneumonitis, bronchitis, or bronchiolitis), thrombocytopenia, jaundice, and abnormal liver function tests may be noted in severe cases. Brill–Zinsser disease is a mild illness with prolonged fever, and a light rash. Most symptomatic rickettsial diseases cause moderate illness, but epidemic typhus and rocky mountain spotted fever can be severe and may be fatal if untreated.

DIAGNOSIS

The clinical findings itself are diagnostic. Fever, headaches, evidence of scratching and skin rash are the usual symptoms which should arouse the suspicion. Circumstantial evidence like unhygienic patients infested with body lice, overcrowding, lack of cleaning facilities as in slum areas are supportive. Thrombocytopenia and an increase of the hepatic enzymes can be observed especially in severe cases. *R. prowazekii* cannot be grown on artificial media and specialized laboratory facilities are required to recover the organism. Diagnosis is usually done clinically and supported by serological investigations. The microimmunofluorescence antibody test is the standard test for the diagnosis of rickettsial disease. It can indicate acute and old infections by IgM generally identified and IgG antibody responses. Causative organism can be specifically identified by serologic testing. In advanced facilities, immunohistochemical analysis and PCR can be helpful.

TREATMENT

Treatment of patients with clinically suspected rickettsial infection should be started immediately and should not await for laboratory confirmation. Doxycycline, chloramphenicol and azithromycin are mainstay of the treatment. Doxycycline is the drug of choice and given in dose of 5 mg/kg/day. Oral treatment is preferred unless patient is vomiting, drowsy or comatose. Therapy should be given for at least 3 days after patient becomes afebrile, or for total 5–7 days. Majority of treated patients improve markedly within 48 hours after initiation of therapy.

PREVENTION AND CONTROL

Delousing is the most important preventive measure for this infection and has been the turning point in controlling the epidemics of typhus. As body lice and their eggs are present in

the clothes, removal and destruction or washing and boiling of all clothes can effectively destroy lice. Application of all clothing with DDT, malathion, permethrin (as in the WHO protocol) is also effective method of killing body lice and reducing re-infestation. Although protective vaccines have been developed, they have not been widely used because effective antibiotic treatments are readily available.

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IN A NUTSHELL

1. Epidemic typhus (caused by *R. prowazekii* and transmitted by lice) is more of historical importance although resurgence is noted in 1997, so instituting hygienic methods and prevention of lice infestation is important.
2. War, famine, refugee camp and jail have reported epidemics of typhus fever.
3. Rickettsial infections are difficult to diagnose and high index of suspicion is essential for early diagnosis and treatment.
4. Fever, maculopapular, hemorrhagic rash, headache, myalgia are initial features of these infections.
5. Therapy should be started at the earliest even with clinical suspicion to avoid morbidity and mortality.
6. Treatment is cheap, affordable and the response to therapy is dramatic. Doxycycline is the drug of choice, and it can be used safely in children.

Chapter 34.5

Murine Typhus (Endemic Typhus)

Govind Benakatti, LH Bidari

Murine typhus, also known as *endemic typhus*, or *flea borne typhus*, is an important cause of acute febrile illness; and is most widely distributed flea borne rickettsial infection worldwide. It is caused by *Rickettsia typhi* and transmitted by infected fleas. Due to lack of awareness, it is the most under-recognized and under-reported illness worldwide. In areas, where febrile illnesses are common, studies have shown that incidence of murine typhus ranges from 0.5% to 6% in various countries. Murine typhus and epidemic typhus (caused by *R. prowazekii*) belong to typhus group rickettsial illnesses. Genomics of *R. typhi* and *R. prowazekii* have similar structures and share similar clinical characteristics, but murine typhus is considered as milder spectrum of disease with favorable prognosis. There are no published literatures from India on this condition.

EPIDEMIOLOGY

R. typhi is primarily transmitted by rat flea *Xenopsylla cheopis* and maintained in rat-flea-rat cycle where rats act as the main reservoirs. Murine typhus is distributed worldwide, largely in tropical and subtropical regions (ports and coastal areas) involving urban environment where high population of rats and domestic rodents are found. Though rat fleas are the primary vectors of transmission, lice and mites also act as potential vectors. Other vertebrate hosts such as house mice, shrews, opossums, skunks, and cats are the reservoirs. Rat and rat fleas do not suffer disease and remain infected lifelong. Murine typhus often follows a seasonal distribution and transmission rate correlates closely with population of rat fleas. Peak incidence of murine typhus occurs around spring and summer in urban areas and fall in coastal areas when fleas are most abundant. Though murine typhus is an endemic illness, outbreaks have been described in literature. It is also been recognized as an important cause of travel acquired rickettsial fever with Africa and Southeast Asia being the most frequent sites of disease acquisition.

ETIOLOGY

R. typhi is transmitted by inoculation of infected flea feces at the bite site and gains entry into the host through contamination of infected site which is facilitated by rubbing or scratching of bite site. When blood feeding fleas feed on the infected reservoir, organism gains entry into the midgut of fleas where they invade and multiply within the gut epithelium. This multiplication eventually leads to rupture of these cells and release large number of rickettsiae into the gut lumen. This process usually takes 3–4 days before recognizable number of rickettsiae can be seen in feces and become the source of infection to the human and other mammalian hosts. Typically fleas become infectious approximately 10 days after they get infected and remain infectious throughout rest of their life.

PATHOGENESIS

R. typhi is a vasculotropic obligate intracellular pathogen just like other rickettsiae. Endothelial cells are the primary target cells and widespread endothelial injury with increased vascular permeability is the hallmark pathophysiologic feature of rickettsial infections. The diversity of microvascular injury explains the wide

spectrum of clinical manifestations. In contrast to other rickettsiae, *R. typhi* has limited intracellular mobility that explains the less severe manifestations of murine typhus.

CLINICAL FEATURES

The incubation period is 7–14 days with average being 10 days. The initial manifestations of murine typhus are often nonspecific with prodromal symptoms of headache, joint pains and persistent fever. Often it presents as *fever without focus* that usually lasts for 3–7 days followed by onset of rash that begins on trunk and spread peripherally. Though rash is the hallmark diagnostic feature of rickettsial diseases, its presence in murine typhus varies from 20% to 80% of cases and absence of rash should not preclude the diagnosis of murine typhus. The characteristics of rash in murine typhus are similar to that in other rickettsial infections as being nonpruritic, macular or maculopapular starting on the trunk and then spreading peripherally, can involve both palms and soles; lasting 1–4 days; and occurring, on an average 1 week after the onset of fever. Less than half (up to 40%) of patients reported to have flea bite site evident on examination. Severe manifestations such as meningoencephalitis, stupor, coma, seizures, hepatitis, myocarditis, endocarditis, multiorgan dysfunction, etc. though less common have been reported. The most common laboratory abnormalities include anemia (18–75%), leukopenia (18–40%), leukocytosis (1–29%), thrombocytopenia (19–48%), elevated ESR (59–89%), and elevated aminotransferase levels (38%–90%), hyponatremia (20–66%), and hypoalbuminemia in 46–89%.

DIAGNOSIS

Differential Diagnoses

Due to its wide spectrum of manifestations and as it most commonly presents as fever of unknown origin; high index of suspicion is needed to diagnose murine typhus at the outset of presentation to the hospital. It is often difficult to distinguish murine typhus from other rickettsioses such as Rocky Mountain spotted fever and scrub typhus. Thus murine typhus should always be considered as a differential diagnosis of fever without focus, and those with fever with maculopapular rash. Differential diagnosis include common causes of fever of unknown origin such as enteric fever, bacteremia, and viral pyrexia and fever with rash such as viral exanthems, rubella, measles, infectious mononucleosis, roseola, and Kawasaki disease, etc. All differential diagnoses discussed in previous two chapters for these illnesses also apply here.

Laboratory Diagnosis

Though many laboratory methods are available; diagnosis and treatment of murine typhus is primarily made on clinical basis. Laboratory diagnosis is sought often for the confirmation of diagnosis. Currently indirect fluorescent antibody test is considered as *gold standard* and most widely used. A titer of more than or equal to 1:64 at the end of first week is considered as diagnostic with sensitivity of 94–100% and specificity of 100%. EIA to detect IgM has sensitivity of 88% and a specificity of 91%. Though Weil–Felix (based on principle of heterophile agglutination with *Proteus* spp.) test has very poor sensitivity and specificity is still the most widely used test in India for diagnosis of rickettsial infection. Murine typhus patient's sera react with OX-19. Other available tests include PCR and serologic assays such as indirect immunoperoxidase assay, latex agglutination and Western blot.

MANAGEMENT

Doxycycline is the treatment of choice (4 mg/kg/day divided 12 hourly PO or IV, maximum 200 mg/day). Effective alternative include; chloramphenicol (50–100 mg/kg/day divided every

6 hours, maximum 4 g/day). Quinolones (ciprofloxacin, ofloxacin) are also effective but associated with higher relapse rate. Macrolides (azithromycin, clarithromycin) are effective alternatives. Therapy is continued minimum of 5 days (usually 3–7 days) or at least 48 hours following defervescence.

PROGNOSTIC FACTORS

Murine typhus is usually considered as a benign self-limiting disease with mortality rate of 1%. It has excellent prognosis provided appropriate antibiotics are used. Delay in diagnosis and treatment is the single most important prognostic factor. However, 5–10% of children do suffer from severe illness such as meningoencephalitis, seizures, coma and multiorgan dysfunction requiring intensive care unit admission. All organ supportive therapy along with strict hemodynamic monitoring and careful fluid management is mandatory to avoid adverse outcome.

PREVENTION

Murine typhus infection can be effectively prevented through flea control measures on pets, especially domesticated cats. Currently no vaccine is available against murine typhus, and it is not known whether infection confers lifelong immunity.

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IN A NUTSHELL

1. Murine typhus (endemic typhus) is one of the most under reported illness distributed worldwide especially in tropical, subtropical regions and coastal ports.
2. *Rickettsia typhi* (causative agent of murine typhus) shares similar genomes and clinical characteristics with *R. prowazekii* (causative agent of epidemic typhus) but is a much less severe form of illness.
3. Although rash is the hallmark diagnostic feature of the rickettsial illnesses, most common initial presentations of murine are nonspecific, and most commonly, it presents as fever without focus. Therefore, it should be considered in the list of differential diagnosis of all common causes of fever of unknown origin.
4. Murine typhus is considered as self-limiting infection with excellent prognosis. Mortality rate is about 1% provided appropriate antibiotics are used. However 5–10% children can have severe manifestations such as meningoencephalitis, splenic rupture, persistent abdominal pain, and endocarditis.
5. Doxycycline is the treatment of choice with chloramphenicol, azithromycin, clarithromycin being the effective alternatives.

Chapter 34.6

Mycoplasma Infections

Tanu Singhal

Mycoplasma are the smallest of free-living life forms with characteristics somewhere between bacteria and viruses. They measure 150–250 nm and lack cell walls, have sterols in the cell membrane, contain both RNA and DNA, have fastidious growth requirements but can grow in cell-free media (**Fig. 1**). The most important species causing human disease is *Mycoplasma pneumoniae*. The genital *Mycoplasmas* (*M. hominis* and *Ureaplasma urealyticum*) are associated with genital tract disease in adults and sometimes neonatal disease.

EPIDEMIOLOGY

Disease due to *Mycoplasma* is prevalent worldwide and occurs in all seasons. It is transmitted from person to person as a droplet infection and hence community, school and family outbreaks are not uncommon. Outbreaks in schools have been attributed to poor ventilation. Newborns can get infected by genital *Mycoplasmas* during delivery. *M. pneumoniae* can infect children of any age but is uncommon in the first year of life. Children less than 3 years usually suffer from an upper respiratory tract infection. The rates of infection and incidence of lower respiratory disease rise with increasing age especially in school-aged children and adolescents where it cause more than one-third of all community-acquired pneumonias (CAP). Children with humoral immunodeficiency, congenital heart disease, Down syndrome and sickle cell disease are likely to have severe and complicated illness.

PATHOGENESIS

Mycoplasma causes infection by attaching to the ciliated and nonciliated epithelium of the respiratory and genital tracts. The attachment protein is a complex carbohydrate similar to the I antigen of the red blood cells. Antibody response to this receptor causes the formation of the I antibody, a cold agglutinin that acts as an autoantibody. Following attachment, *Mycoplasma* causes damage by direct cytolysis or immune-mediated reaction. Systemic spread of *Mycoplasma* does not occur and the extrapulmonary manifestations are due to an immune-mediated mechanism.



Figure 1 Fried-egg colonies of *Mycoplasma* on agar media

CLINICAL FEATURES

The most common manifestations of *Mycoplasma* disease are low-grade fever, cough, headache, malaise, pharyngitis, rhinorrhea and sometimes otitis media. Bullous myringitis is a classic but rare manifestation of *Mycoplasma* infection. Wheezing is common especially in asthmatic children. Acute asthma may be the first presenting manifestation. The cough is insidious in onset, worsens over the next few days and can be quite debilitating. Only a minority of the infected children (especially those who are older), suffer from lower respiratory disease and pneumonia. Tracheobronchitis and bronchopneumonia are the most frequently reported severe manifestations. Pneumonia is associated with few clinical signs and is of varying severity. Patients rarely appear ill and hence the term *walking pneumonia*. There is marked disparity between the clinical symptoms and signs and the radiographic picture. The radiographic picture is variable; the most common finding is thickened bronchial shadow, streaks of interstitial infiltration, and areas of atelectasis primarily in lower lobes. There may be hilar adenopathy and pleural effusion. In some children, fulminant pneumonia and respiratory failure may occur.

Extrapulmonary manifestations can coexist/follow/occur independently of respiratory disease. The commonest extrapulmonary manifestations are dermatologic and include an erythematous macular and/or morbilliform rash or a papulovesicular exanthem or erythema nodosum. In some patients, erythema multiforme or Stevens-Johnson syndrome may occur. *Neurologic manifestations* include encephalitis, aseptic meningitis, transverse myelitis, peripheral neuropathies and radiculopathies, brainstem dysfunction, dysfunction of the pyramidal or extrapyramidal tract, cerebellar dysfunction, cerebral infarction and Guillain-Barré syndrome. *Mycoplasma* should be suspected as a cause of acute febrile encephalopathy especially if there are preceding or coexistent respiratory manifestations. Cold antibody mediated immune *hemolytic anemia* is another complication which may be vary from subclinical hemolysis to life-threatening hemolytic anemia. Rarely the gastrointestinal tract (GIT), heart, kidneys and joints may be involved. Neonates with genital *Mycoplasma* infection may present with cough/wheezing or sepsis, meningitis and brain abscess.

DIFFERENTIAL DIAGNOSIS

Respiratory *Mycoplasma* infections should be differentiated from pneumococcal and respiratory viral infections (influenza, parainfluenza, adenovirus, respiratory syncytial viral infections) and other atypical pneumonias. Central nervous system (CNS) *Mycoplasma* infections should be differentiated from other causes of acute febrile encephalopathy.

DIAGNOSIS

Complete blood count shows anemia, leukocytosis with neutrophilia and elevated erythrocyte sedimentation rate (ESR). Liver transaminases can be mildly elevated. In CNS disease, there is lymphocytic pleocytosis, elevated protein and normal glucose in the cerebrospinal fluid (CSF). The peripheral smear may show rouleaux formation due to the cold agglutinins and may be a pointer towards diagnosis (**Fig. 2**). Incubating the serum of the patient with type O erythrocytes at 4°C and observing for agglutination that reverses at 37°C indicates the presence of cold agglutinins. The sensitivity and specificity of cold agglutinins in *Mycoplasma* disease is around 50%. Higher the cold agglutinin titer, higher is the specificity.

Specific diagnosis is possible by demonstration of anti-*Mycoplasma* immunoglobulin M (IgM) by enzyme-linked immunosorbent assay (ELISA). IgM antibodies appear usually 7 days after infection and may be negative in early disease. They remain elevated for a long-time. *Mycoplasma*-specific polymerase chain

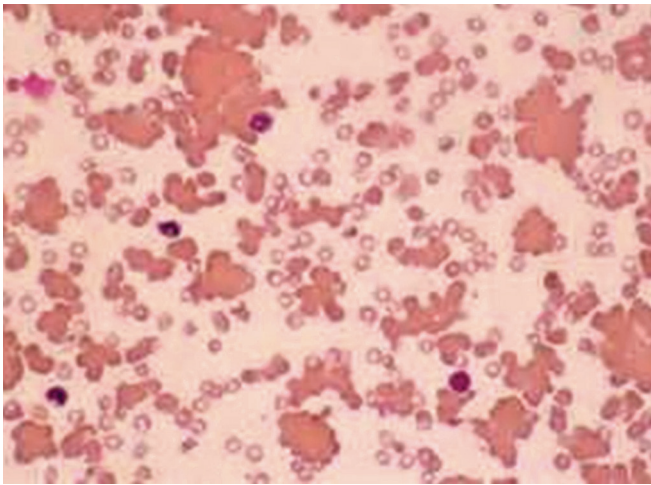


Figure 2 Peripheral smear showing red cell agglutination in *Mycoplasma* disease

reaction (PCR) from respiratory secretions is very sensitive and specific but expensive and not easily available. Most multiplex PCR kits for diagnosis of respiratory infections include *Mycoplasma* PCR.

TREATMENT

Respiratory Disease

Empirical therapy for *Mycoplasma* is recommended for all children especially those above 5 years with CAP where clinical features suggest *Mycoplasma*/atypical pathogens and in those children with CAP who do not respond to beta-lactam drugs. In children especially those more than 5 years with severe or very severe disease, empirical therapy with macrolides at the outset may be considered irrespective of clinical features. Treatment of acute asthma exacerbations with macrolides in view of the relationship between *Mycoplasma* and wheezing has no demonstrable benefit.

Since *Mycoplasmas* lack cell walls, all cell wall active antibiotics including beta-lactams are inactive. Macrolides are the drugs of choice for *Mycoplasma*. Recommended regimens include azithromycin 10 mg/kg in one dose on the first day and 5 mg/kg in one dose for 4 days, clarithromycin 15 mg/kg/day in two divided doses for 10 days, or erythromycin 30–40 mg/kg/day in four divided doses for 10 days. Azithromycin and clarithromycin have the advantages of less frequent dosing and fewer gastrointestinal disturbances.

In children older than 8 years, tetracycline 20–50 mg/kg/day in four divided doses (maximum daily dose 1–2 g) or doxycycline 2–4 mg/kg/day in one or two divided doses (maximum daily dose 100–200 mg) for 10 days also is effective.

M. pneumoniae resistant to macrolides has been reported from various countries. Prolonged fevers may occur in children with macrolide-resistant isolates who are treated with macrolide antibiotics. The possibility of macrolide resistance should be considered in children with suspected *M. pneumoniae* infection who do not respond as expected to macrolide therapy. Tetracyclines in doses detailed above and fluoroquinolones (e.g., levofloxacin) are alternative treatments for macrolide-resistant strains. Fluoroquinolones should only be used in children younger than 18 years if the benefits of therapy exceed the risks. Information regarding levofloxacin dose in children is limited.

Extrapulmonary Disease

Mycoplasma should be considered as a cause of acute febrile encephalopathy/encephalitis in children especially if there

is a coexisting or preceding respiratory illness. The role of antimicrobials is uncertain as pathology appears to be immune-mediated treatment modalities of uncertain efficacy that have been used in this setting include antimicrobials, steroids, diuretics, anti-inflammatory drugs, intravenous immunoglobulin (IVIG) and plasma exchange. Antimicrobials with good CNS penetration like fluoroquinolones and chloramphenicol may be considered. Severe hemolytic anemia has been treated with warming, steroids and plasma exchange. *Mycoplasma* should be suspected as a cause of neonatal sepsis in a setting of nonresponse to standard antibiotics in neonatal sepsis/respiratory disease.

PROGNOSIS

The outcome of pulmonary disease is generally good; no accurate data is however available. Acute complications include necrotizing pneumonia, acute respiratory distress syndrome (ARDS) and long-term complications include possible predisposition to recurrent wheezing and reduced lung function. Most cases with CNS complications recover though mortality and long-term sequelae may occur.

IN A NUTSHELL

1. *Mycoplasma* is a common cause of lower respiratory illness in older children and adolescents.
2. Specific diagnosis of disease on the basis of clinical manifestations is difficult. Laboratory diagnosis can be attempted by detection of specific IgM antibodies by ELISA.
3. Empirical therapy for *Mycoplasma* with macrolides should be considered in older children/adolescents with CAP not responding to beta-lactam antibiotics or at the outset in severe disease.
4. Corticosteroids are used in the therapy of severe disease particularly in CNS complications.

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Chapter 34.7

Chlamydial Infections

Sulochana Putali Bai

Chlamydia are obligate intracellular bacterial pathogens whose entry into mucosal epithelial cells is required for their intracellular survival and growth. It causes a variety of diseases in animal species like birds, reptiles and mammals. The most common human pathogens are *Chlamydia pneumoniae* and *Chlamydia trachomatis*.

MICROBIOLOGY

The family Chlamydiaceae consists of two genera: *Chlamydia* and *Chlamydophila*. One species of *Chlamydia* and two of *Chlamydophila* are important in causing disease in humans.

- *Chlamydia trachomatis* can cause urogenital infections, trachoma, conjunctivitis, pneumonia and lymphogranuloma venereum (LGV).
- *Chlamydophila pneumoniae* can cause bronchitis, sinusitis, pneumonia and possibly atherosclerosis.
- *Chlamydophila psittaci* can cause pneumonia (psittacosis).

Members of the Chlamydiaceae are small obligate intracellular bacteria. They depend on the host cell for ATP as they are unable to produce them. Their inner and outer membranes are similar to gram-negative bacteria and the membrane contains lipopolysaccharide but does not have a peptidoglycan layer. *Chlamydia* are susceptible to antibiotics that interfere with DNA and protein synthesis, including tetracyclines, macrolides and quinolones. *Chlamydia* exists in two distinct morphological forms:

1. Elementary body (EB) which is the infectious form. EBs are small (0.3–0.4 μm) and possess a rigid outer membrane that is extensively cross-linked by disulfide bonds. They are considered similar to spores because they are metabolically inactive and due to their rigid outer membrane, the elementary bodies are resistant to harsh environmental conditions outside their eukaryotic host cells. The elementary bodies bind to receptors on host cells (epithelial cells) and initiate infection.
2. Reticulate body (RB) which is the reproductive form. RBs are the noninfectious intracellular form of the *Chlamydia*. They are different from the EBs as they are metabolically active replicating form of the *Chlamydia* and they possess a membrane which lacks extensive disulfide bonds.

PATHOGENESIS

During chlamydial infection, the infectious EBs attaches to the host cell and are internalized by endocytosis and/or by phagocytosis. EBs remain within a phagosome by inhibiting phagosomal lysosomal fusion. The complete intracellular life cycle of the *Chlamydia* occurs within the phagosome. The EB transforms into a RB, within 8 hours and RBs begin to multiply by binary fission within an isolated area called an inclusion. After approximately 36 hours, the RBs differentiate back into EBs. The inclusion may contain 100–500 EBs per inclusion. After 48 hours EBs are released by exocytosis (extrusion of whole inclusion in *C. trachomatis* and *C. pneumoniae*) leaving the host cell intact or by cytolysis (*C. psittaci*).

Chlamydia may enter into a persistent state after treatment with IFN- γ or penicillin and due to lack of certain nutrients. It shows decreased metabolic activity, loss of infectivity, small inclusions with less numbers of EBs (altered inclusions) and refraction to

antibiotic treatment during the persistent state. *Chlamydia* have been shown to modulate cellular apoptosis (induce or inhibit based on the stage of developmental cycle) for their survival and replication. *Chlamydia* protects infected cells against apoptosis during initial stages of infection and induces apoptosis of host cell during final stages of the developmental cycle. The altered inclusions and inhibition of apoptosis may be the mechanisms of persistent infection.

CHLAMYDOPHILA PNEUMONIAE INFECTION

Chlamydophila pneumoniae (formerly known as *C. pneumoniae*) is a human respiratory pathogen associated with otitis media, sinusitis, bronchitis, pneumonia, pharyngitis, chronic obstructive pulmonary disease, asthma and atherosclerosis.

Epidemiology

C. pneumoniae is distributed worldwide. The prevalence increases with age; the seroprevalence rate sharply increases between 5 years and 20 years reaching more than 70% in adults. Reinfection is highly common even with such high prevalence. The organism is transmitted from human to human by infected respiratory secretions. It commonly spreads within families and enclosed population.

Pathophysiology

Acute infection of the lung due to *C. pneumoniae* causes acute patchy pneumonia with infiltrates in the alveoli and interstitial tissue of the lung. It is characterized by alveolar edema and mononuclear infiltrate. Reinfection by *C. pneumoniae* is common and characterized by interstitial pneumonia. In certain pneumonia cases, *C. pneumoniae* may not be the primary pathogen but its infection may have disrupted the normal clearance mechanisms and would have enabled other respiratory pathogens, like pneumococci to invade and cause pneumonia.

Clinical Features

Most *C. pneumoniae* infections are mild and asymptomatic but in few cases it has been fatal. In symptomatic infection the onset is gradual and presents initially with fever and pharyngitis which develops into cough and pneumonia over a week. Wheeze and crackles may be present resembling viral associated wheeze. It is one of the causes of atypical pneumonia resembling *Mycoplasma pneumoniae*. Clinically pneumonia due to *C. pneumoniae* is indistinguishable from other pneumonias. *C. pneumoniae* often causes persistent subclinical infection for many months to years. Many studies have found association between *C. pneumoniae* infection and asthma but the basis for this is not clear.

Diagnosis

Clinical features of pneumonia due to *C. pneumoniae* resemble *Mycoplasma pneumoniae* and influenza infection. Erythrocyte sedimentation rate (ESR) is generally elevated and peripheral WBC count is either normal or increased with neutrophil predominance. Chest X-ray may show findings out of proportion to the clinical status and might include diffuse bilateral involvement or lobar shadows with or without pleural effusion. Isolation of *C. pneumoniae*, antigen detection and detection of DNA by polymerase chain reaction (PCR) from respiratory specimens [throat swab, nasopharyngeal swab, bronchoalveolar lavage (BAL), sputum] and serology are the methods available to detect *C. pneumoniae* infections. The isolation of *C. pneumoniae* in cell culture is technically demanding. Detection of antigen by direct immunofluorescence requires technical expertise and is subjective. Molecular method of detection of *C. pneumoniae* is under evaluation. Detection by culture or antigen test or PCR

does not confirm recent infection as long-term shedding of *C. pneumoniae* is observed in many patients.

Serology is commonly used for routine diagnosis of *C. pneumoniae* infections due to its easy availability and simplicity. Microimmunofluorescence (MIF) test is the commonly used method. Anti *C. pneumoniae* IgM titer of more than or equal to 1:16 or a fourfold rise in IgG titer between acute and convalescent serum specimens confirms acute primary infection. Serological tests have a sensitivity of 60–80% and specificity of 90–100%.

Treatment

C. pneumoniae is susceptible to tetracyclines, macrolides, quinolones and ketolides. Resistance is not common. The following regimen is recommended for treating *Chlamydia pneumoniae* infection in children:

- Azithromycin 10 mg/kg/once a day followed by 5 mg/kg/once daily for 4 days
- Erythromycin 50 mg/kg/day for 10–14 days
- Clarithromycin 15 mg/kg/day for 10 days.

Therapy with antichlamydial antibiotics in patients with asthmatic exacerbations, in whom CP infection is proven or presumed, has shown beneficial effects. This may be due to the antichlamydial effect or immunomodulatory effect of the antibiotics. Antibiotics are highly effective in treatment of acute *C. pneumoniae* infections but their effectiveness for treating chronic infections is limited.

Prevention

Currently there is no vaccine is available for prevention of *C. pneumoniae* infection but evaluation of various antigens for a potential vaccine is underway.

IN A NUTSHELL

1. Children with chlamydial infections usually present with features of lower respiratory infection.
2. It is one of the causes of atypical pneumonia and can present with wheeze.
3. Macrolides are the drugs of choice for therapy.

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PART VIII Systemic Disorders

Section 35 GASTROINTESTINAL DISORDERS

Section Editors A Riyaz, John Matthai

Chapter 35.1

Anatomy and Physiology

S Arivu Selvan

The gastrointestinal tract (GIT) constitutes the esophagus, the stomach and the small and large intestines. The esophagus serves as a passage for food from the mouth and pharynx to the stomach. The stomach is the site where the food is thoroughly mixed with gastric secretions. It aids emptying the contents into the duodenum. Absorption of digested food occurs mainly in the small intestine. The liver and pancreas form the major glands of the digestive system. They discharge their secretion into the duodenum. Fecal matter is formed in the descending and sigmoid colons and is collected in the rectum before defecation through the anal canal.

Gastrointestinal tract plays a prominent role in immune function. The low pH of the stomach, and the mucus secreted from it are lethal to microorganisms entering the gut. The enzymes in saliva and bile are other factors helping with immune function. *Helicobacter pylori* are the only bacteria found alive in the stomach. They are considered responsible for gastritis and gastric ulcers.

The microorganisms forming the beneficial flora of the gut prevent overgrowth of harmful bacteria by competing for space and food. A ratio of 4:1 between the beneficial and harmful bacteria is generally considered normal within the intestines. The *gut-associated lymphoid tissue* (GALT) plays a vital role in killing the organisms entering the gut.

DEVELOPMENT OF THE GUT

The development of gut occurs at the beginning of the 4th week of gestation. The trilaminar embryonic disc with the three germ layers is folded upon itself cranially, caudally and side-wise. As a result, the endodermal layer of the disc becomes tubular and forms the inner lining of the gut. During this process, most of the yolk sac communicating with the gut is incorporated into it and contributes to formation of gut. The remaining part of the yolk sac with the vitellointestinal (omphaloenteric) duct (**Fig. 1**) later disappears. Persistence of the vitellointestinal duct gives rise to the *Meckel's diverticulum*.

Following folding of the disc, two pits known as stomatodeum and proctodeum develop at the cranial and caudal ends of the gut respectively. Initially, the two ends of the gut are separated from these pits by the buccopharyngeal and the cloacal membranes, respectively (**Fig. 2**). Later, these membranes rupture and the gut communicates with the exterior at these ends. Failure of rupture of the cloacal (anal) membrane results in *imperforate anus*.

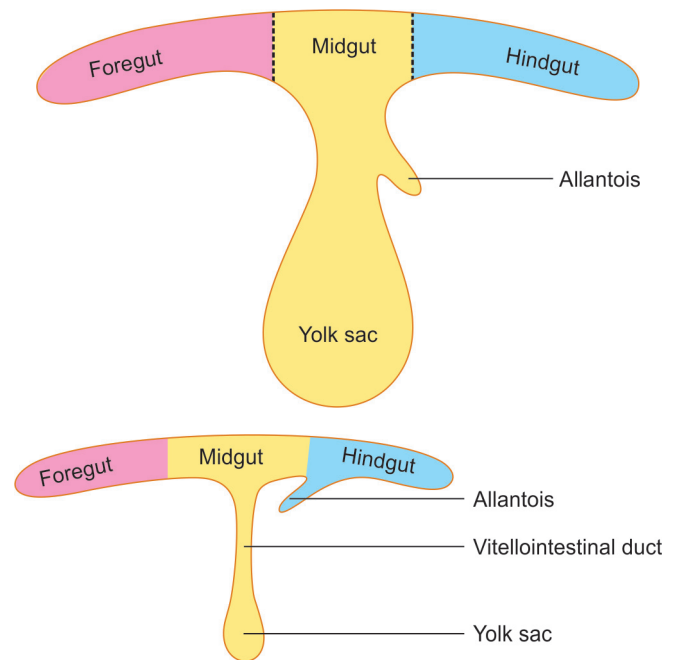


Figure 1 Formation of primitive gut following folding of the embryo

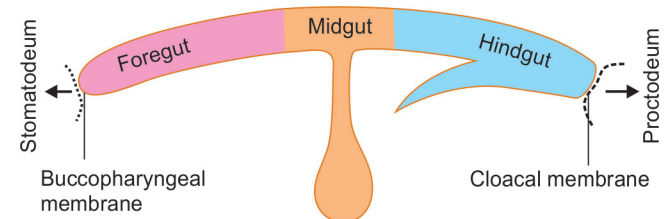


Figure 2 Formation of cranial and caudal pits (stomatodeum and proctodeum)

The foregut gives rise to the upper part of the alimentary canal from the floor of the mouth down to the level of upper part of duodenum marked by the major duodenal papilla. The midgut begins at this level and ends at the junction between the right two-thirds and left one-third of transverse colon. The remaining part of the gut down to the anal canal above the pectinate line is contributed by the hindgut. The lower part of anal canal develops from proctodeum.

The endoderm gives rise to the epithelial lining of the gut; the other layers of the gut are derived from the splanchnopleuric mesoderm surrounding the gut. The glands of the digestive tract and their duct system develop from the foregut as buds or diverticula. During early stage of development, the cells of the neural crest migrate into the wall of the gut and form the enteric nervous system (ENS). *Achalasia cardia* and *congenital megacolon* (Hirschsprung disease) are due to failure of migration of neural crest cells to form the nerve plexuses in the respective parts of the gut.

Rotation of Midgut Loop

In the initial stage, the abdominal cavity is largely occupied by the massive liver and kidneys. There is only little space within the peritoneal cavity to accommodate the rapidly elongating coils of intestines. As a result, during 6th week of development, the midgut loop herniates into the umbilical cord. This is known as *physiological umbilical herniation* and is a normal event in all embryos. Elongation of intestines occurs outside the body.

During 10th week of development, when the abdominal cavity becomes sufficiently larger, the whole of the herniated bowel is withdrawn into the abdominal cavity. During the process of herniation and withdrawal, the midgut loop undergoes 270° rotation in anticlockwise direction. This rotation of the midgut is essential to establish appropriate positions of parts of gut within the peritoneal cavity. Failure of return of the midgut results in *omphalocele* or *exomphalos*. Similarly, incomplete rotation (mixed rotation), rotation in the opposite direction (reversed rotation) or failure of rotation (nonrotation) gives rise to various anomalies associated with abnormal position of parts of the gut in the abdominal cavity (e.g., presence of cecum in the midline below the stomach). Such abnormal positions of the parts of gut are prone to intestinal obstruction due to *volvulus*.

Fixation of the Gut

Initially, the gut is suspended from the posterior abdominal wall by a fold of peritoneum known as the dorsal mesentery. Later, alternate parts of the gut lose their mesentery and become retroperitoneal. Fixation of the gut is essential to retain its appropriate position in the abdominopelvic cavity and to prevent intestinal obstruction due to *volvulus*. The parts of the gut that lose their mesentery include the duodenum except its first part, the ascending colon and descending colon, the rectum and the anal canal. The cecum is covered with peritoneum on all sides. However, it does not have a mesentery.

DEVELOPMENT OF LIVER AND GALLBLADDER

The liver develops as a diverticulum (hepatic bud) extending from the lower part of foregut. This diverticulum soon bifurcates into two parts: pars cystica and pars hepatica. The pars cystica expands to form the gallbladder and the pars hepatica expands to form the parenchyma of the liver (**Fig. 3**). The proximal parts of the diverticulum remain narrow and form the biliary ducts. The stroma of the liver such as sinusoids, Kupffer cells and capsule develop from the *septum transversum*, a fibrous septum that forms part of the diaphragm.

DEVELOPMENT OF PANCREAS

The development of pancreas is marked by two pancreatic buds: ventral and dorsal extending from the lower part of the foregut close to the hepatic diverticulum. Due to rotation of the stomach and differential growth of the duodenum, the buds come closer and fuse to form the pancreas (**Fig. 4**). Insulin secretion begins from 10th week of development. Variations in the formation

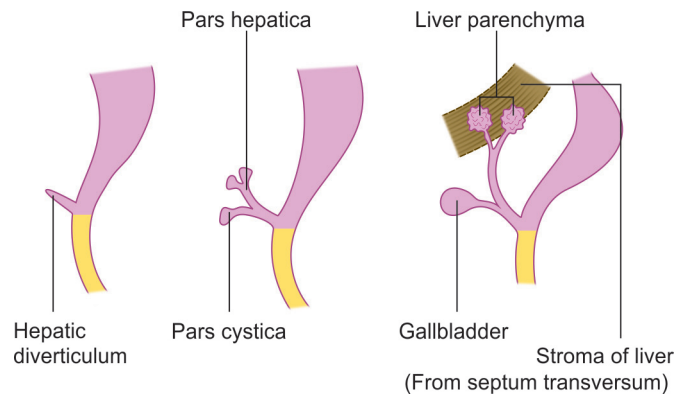


Figure 3 Development of hepatobiliary apparatus

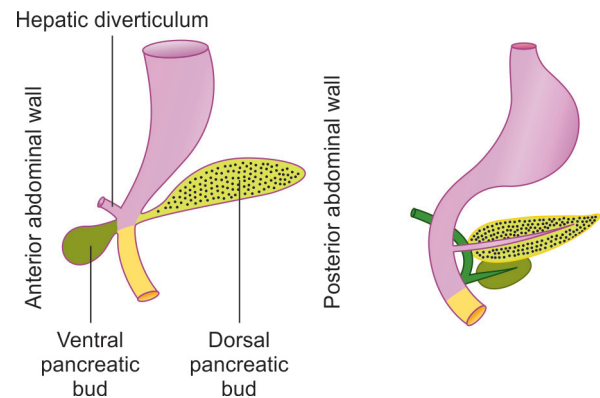


Figure 4 Development of pancreas

and mode of termination of the biliary and pancreatic ducts are common. In some cases, the bile duct and the pancreatic duct fail to unite and open independently into the duodenum. *Annular pancreas* is a developmental anomaly in which a ring of pancreatic tissue surrounds the second part of the duodenum. A bifid ventral pancreatic bud is attributed to be a cause of this anomaly.

BLOOD SUPPLY OF THE GUT

The aorta running behind the gut gives off several branches to the gut in the initial stage of development. Later, many of these branches disappear and only three arteries persist. The celiac trunk supplies the foregut from the lower part of esophagus, liver, gallbladder and pancreas, which are the derivatives of the foregut; the superior mesenteric artery (SMA) supplies the midgut and the inferior mesenteric artery (IMA) supplies the hindgut.

Since the duodenum develops from both the foregut and the midgut, it is supplied by the branches of celiac trunk and SMA. The branches of these arteries anastomose to form an arterial arcade around the head of the pancreas. This anastomosis provides an alternative source of blood to the foregut structures in case of occlusion of celiac trunk or its branches.

Since the transverse colon marks the junction between the midgut and the hindgut, it is supplied by both the midgut (SMA) and the hindgut (IMA) arteries. The branches of these arteries anastomose freely and form a circumferential artery known as the *Marginal artery of Drummond* along the inner margin of the colon. This artery supplies the entire colon. In cases of occlusion of the

SMA or IMA, this anastomosis helps to provide blood to the affected part of the colon. However, the area near the splenic flexure where the branches of the two gut arteries meet is least vascular and it becomes a common site of *ischemic necrosis* of colon.

The *jejunum and ileum* are supplied by 15–18 branches arising from the SMA. They unite to form loops or arches called *arterial arcades*, from which straight arteries known as *vasa rectae* arise to supply the jejunum and ileum. These arteries are end arteries to the jejunum and ileum. Therefore, occlusion of *vasa rectae* due to internal hernia or compression by a tumor can produce *gangrene* of the small bowel.

The appendicular artery supplying the appendix ends even before reaching its tip in most of the cases. Therefore, the tip becomes least vascular and suffers gangrenous changes first in *acute appendicitis*.

The veins draining the gut form the *portal venous system*. The superior and inferior mesenteric veins collect blood from the midgut and the hindgut respectively. The veins from the foregut, pancreas, spleen and most of the gallbladder empty their blood into the portal vein either directly or indirectly through the splenic vein. The portal vein carries blood to the liver through its hilum. This blood after undergoing metabolic changes and detoxification in the liver is emptied into the inferior vena cava through hepatic veins that emerge from the liver.

Unlike the systemic veins, the veins of the portal system are devoid of valves. Therefore, blood flow can occur in either direction depending on pressure changes. The veins of the portal system anastomose with systemic veins (portosystemic anastomosis) in five regions of the abdomen. In portal obstruction or hypertension due to cirrhosis of liver, the blood flow through the liver slows down and blood backs up throughout the portal system. The tributaries of the portal venous system are very much engorged at the sites of portosystemic anastomoses.

INNERVATION OF THE GUT

The GI tract is innervated by both intrinsic innervation through ENS, and extrinsic innervation through autonomic nervous system. ENS referred to as the *minibrain of the gut* organizes and coordinates the activity of musculature, glands, and blood vessels of the gut. Functionally, it consists of three types of neurons: motor, sensory and interneurons. Musculomotor neurons (excitatory and inhibitory) control the contraction and relaxation of musculature of the gut. Secretomotor neurons control the secretory activities of the glands; the sensory neurons receive information regarding the state of the gut, and the interneurons form information-processing networks through their synaptic interconnections. The neurons of the ganglia and their fibers form the two nerve plexuses of the ENS. *Myenteric (Auerbach's) plexus* is primarily concerned with initiation and control of smooth muscle contraction and relaxation such as peristalsis. *Submucosal (Meissner) plexus* coordinates reflexes associated with secretion and absorption, as well as motor control of smooth muscle. Both these plexuses communicate freely within the wall of the gut.

The *parasympathetic fibers* innervating the foregut and midgut originate from the dorsal vagal complex (cranial outflow) in the medulla. The parasympathetic fibers innervating the hindgut originate from the S₂, S₃, S₄ spinal segments (sacral outflow). They form the pelvic splanchnic nerves (*nervi erigentes*). The parasympathetic innervation exerts both excitatory and inhibitory effects on the gut. The efferent vagal fibers synapsing with neurons in the ENS activate circuits to the effector systems. In the case of musculature, they exert reciprocal control over both inhibitory and excitatory musculomotor neurons. These neurons send signals to the musculature of gut both in anticipation of food intake and

following a meal. In the case of glands, the secretomotor neurons are activated to stimulate secretion of the glands. The afferent vagal fibers (visceral afferents) send signals from the gut to the ENS in response to distension of the gut from food. These vagal afferent neurons are connected with a variety of sensory receptors (physical, chemical, and thermal) in the gut. They detect physical parameters such as brushing of mucosa with food, changes in muscle tension, and changes in chemical parameters such as pH, glucose concentration and osmolarity.

The *sympathetic fibers* innervating the gut innervate mainly the blood vessels to produce vasoconstriction, and also mucosa, and musculature of the gut. They suppress gut activity when stimulated. Sympathetic suppression of digestive functions, including motility and secretion, occurs secondary to reduced blood flow mediated by the *norepinephrine* released from sympathetic postganglionic neurons. It acts directly on sphincteric muscles (*lower esophageal sphincter* and *internal anal sphincter*) to keep them closed by increasing their tension.

MICROSCOPIC STRUCTURE OF THE GUT

The wall of the GIT consists of four major layers: mucosa, submucosa, muscularis propria, and serosa (if covered with peritoneum) or adventitia (if not covered with peritoneum). The mucosa, in turn, consists of a lining epithelium, lamina propria of loose connective tissue and muscularis mucosae, a thin layer of smooth muscle. The mucosa differs considerably from region to region based on functional changes in different parts of the gut.

Stomach

The tall columnar epithelium lining the stomach invaginates to form the gastric pits, into which the gastric glands secrete. The gastric glands are composed of four types of epithelial cells:

1. *Mucous neck cells* secrete mucus, which forms a thick lining of about 1 mm thickness on the luminal surface.
2. *Chief cells* produce pepsinogen, a precursor of the proteolytic enzyme pepsin.
3. *Parietal cells (or oxyntic cells)* secrete the gastric acid. In addition to activating the pepsinogen, the gastric acid effectively sterilizes the contents of the stomach. They also secrete *intrinsic factor*, which is necessary for the absorption of vitamin B₁₂.
4. *Argentaffin cells (unicellular endocrine glands)* are found scattered throughout the epithelium of the GIT. They include gastrin-producing cells (*G cells*) and somatostatin-producing cells (*D cells*). *G cells* stimulate the secretion of acid and pepsinogen. *D cells* are activated by acid in the lumen of the stomach and duodenum. They inhibit *G cells* and thereby acid production.

Other types of endocrine cells include vasoactive intestinal polypeptide (VIP)-producing cells (or *D1 cells*) and serotonin-containing cells (enterochromaffin cells). Endocrine cells in the GIT are alternatively named *amine precursor uptake and decarboxylation (APUD) cells*.

Small Intestine

The intestinal mucosa contains numerous *villi*. Each *enterocyte* or the lining epithelial cell forms several *microvilli (brush border)*. The simple tubular glands of intestine (*crypts of Lieberkühn*) open between the villi. Four types of cells are found throughout the mucosa of the intestinal villi. Some have absorptive function while others secrete digestive enzymes and mucus to protect the intestinal lining from digestive actions. The following are the cell types: (1) *simple columnar absorptive cells*; (2) *goblet cells producing protective mucus*; (3) *Paneth cells*, producing lysozyme

capable of digesting bacterial cell walls; and (4) *argentaffin* or enteroendocrine cells, which produce gut hormones like *cholecystokinin* and *secretin*. Cholecystokinin stimulates the secretion of digestive enzymes in the pancreas and the contraction of the gallbladder. Secretin stimulates the pancreas to release *pancreatic juice*. It also augments the effects of cholecystokinin.

The crypts of Lieberkühn secrete the *intestinal juice* (*succus entericus*). A few enzymes are found in the intestinal juice. These include the *amylase* and the *enteropeptidase* (enterokinase). The latter activates the pancreatic enzyme trypsin which in turn activates all proenzymes secreted by pancreas to their active forms. The lymphocytes in the lamina propria form solitary lymphoid nodules known as *Peyer's patches* in the ileum.

The duodenum is characterized by the presence of the *glands of Brunner* in the submucosa; their secretion protects the duodenal mucosa just like the mucus in the stomach.

The lacteals are the specialized lymphatic vessels found in the intestinal villi. They absorb the end-products of fat digestion. They empty their milk-like fluid into the lymphatic plexuses in the walls of the jejunum and ileum.

Large Intestine

Since the mucosa of large intestine is devoid of villi, the mucosal surface is flat with several deep intestinal glands. It contains numerous goblet cells that secrete mucus to lubricate fecal matter as it solidifies. It harbors several kinds of bacteria that help breaking down of molecules, which the gut is not able to break down itself. This is an example of symbiosis. Colon is sterile at birth; colonization of bacteria occurs within a few hours. This is essential for digestion and formation of vitamin K. Further, the intestinal flora helps in the synthesis of vitamin B complex. These bacteria also account for the production of gases.

Liver

The parenchyma of liver is composed of several *hepatic lobules*. Each hepatic lobule is a hexagonal structural unit with hepatocytes arranged in the form of sheets or cords radiating outward from a central vein like the spokes of a wheel. Located between the hepatic cords are the sinusoids, which receive blood at the periphery of the lobule from the portal vein and the hepatic artery and, after traversing the lobule, discharge the blood into the central vein at the center of the lobule. The sinusoids are lined with endothelial cells and contain the stellate cells of Von Kupffer. Bile capillaries (canaliculi) are formed between adjacent hepatic cells, which drain toward the periphery of the hepatic lobule into a bile ductule in the portal canal. This structural unit of the liver is repeated throughout the liver.

Another way of considering the function is a triangular or biliary unit known as *portal lobule*, the corners of which are formed of three central veins. This approach emphasizes the secretion of bile and the biliary system; bile from the canaliculi drain into bile ductules at the center of the triangular unit (portal lobule) (Fig. 5).

The third unit of structure/function is the *hepatic acinus*. Each acinus is a diamond-shaped unit connecting the two adjacent hepatic lobules. The central veins are located at the diametrically opposite angles and portal triads are located at the other two diametrically opposite angles of the diamond. Each hepatic acinus is divided into three *zones*. There is an oxygen gradient (from high to low) between zones 1, 2 and 3. The cells of the zone 3, being least oxygenated are the first to undergo necrosis due to ischemia or drug reaction. After a meal, glycogen will be stored first in the zone 1, later in zone 2, and finally in zone 3. The reverse is true when glucose is needed: zone 3 is depleted of its glycogen first, followed by zones 2 and 1.

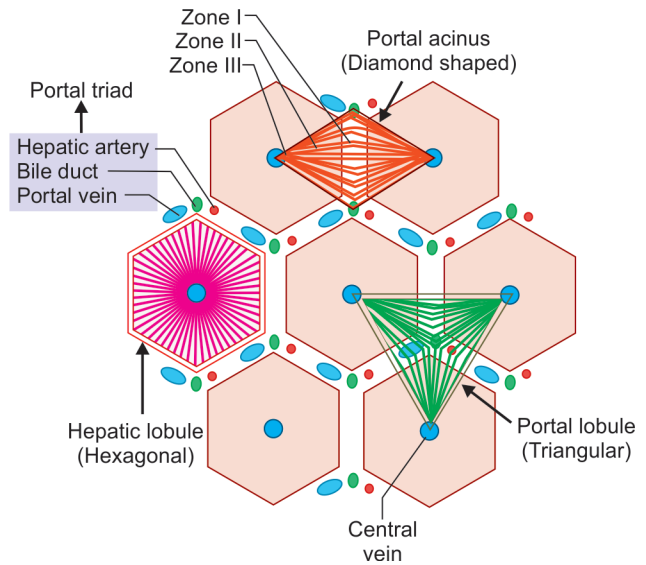


Figure 5 Anatomic and functional lobules of liver

Pancreas

Pancreas is subdivided into several lobules separated by connective tissue septae. Each lobule consists of several compound tubuloalveolar glands with purely serous alveoli. The glandular epithelium consists of pyramidal cells, which secrete zymogen granules into a system of ducts. The centroalveolar or centroacinar cells lie between the secretory cells and the lumen of the alveolus. Interspersed between the exocrine parts of the pancreas are the cells of islets of Langerhans. They are found in abundance near the tail end of the pancreas. Four types of cells constitute the islets: *alpha cells* secreting glucagon, *beta cells* secreting insulin, *delta cells* secreting somatostatin and *PP cells* secreting pancreatic peptide.

IN A NUTSHELL

1. In addition to digestion and absorption of food, the GIT plays significant role in immune function.
2. The liver, the gallbladder and the pancreas including the respiratory tract and the lungs develop as diverticula from the wall of the foregut.
3. Elongation of the intestines occurs outside the body of the embryo and the midgut loop undergoes 270° rotation in the anticlockwise direction during this process. Failure of return of the midgut to the abdominal cavity after elongation results in omphalocele or exomphalos.
4. During initial stage of development, the entire gut is suspended from the posterior abdominal wall by the dorsal mesentery and is therefore intraperitoneal in position. Later, alternate parts of the gut lose their mesentery and become retroperitoneal. The fixation of the gut in this manner is essential to retain their appropriate position in abdominal cavity and to prevent intestinal obstruction such as volvulus.
5. Besides the nerve plexuses of the ENS, the sympathetic innervation to the gut is provided by T5-T6 to L2-L3 spinal segments and the parasympathetic innervation is provided by the vagus and the pelvic splanchnic nerves (S2, S3, S4).
6. Pain impulses from the gut down to the middle of the sigmoid colon are conveyed through the sympathetic fibers and, caudal to this level by the parasympathetic fibers.
7. From within outward, the mucosa, submucosa, muscularis externa and serosa or adventitia are the four major layers forming the wall of the gut.

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Chapter 35.2

Common Symptoms of Gastrointestinal Diseases

Sarah Paul, John Matthai

Symptoms related to gastrointestinal (GI) system are common in children. In most cases, they are indicative of a mild disease, while in some, they are pointers to serious underlying disorders. Not infrequently, they are functional, psychogenic or stress-related. While systemic diseases may manifest with abdominal symptoms, GI diseases need not always have symptoms referable to the GI tract. A basic understanding of the pathophysiology of the common signs and symptoms will help avoid unnecessary investigations and parental anxiety.

DIARRHEA AND DYSENTERY

Increase in frequency, fluidity and volume of feces in relation to the age of the child is called diarrhea. In epidemiological studies, diarrhea is defined as the passage of three or more loose or watery stools during a 24-hour period, a loose stool being one that would take the shape of a container. The most common type is the acute watery diarrhea where the illness starts acutely, lasts less than 14 days (most episodes last less than 7 days), and involves the passage of frequent loose or watery stools without visible blood. Diarrhea with visible blood in the feces is called dysentery and signifies inflammation of the intestinal mucosa. Children appear sick and systemic signs like fever, anorexia and abdominal pain last much longer.

Watery stools are common in either osmotic or secretory diarrhea. Small bowel mucosa is a porous epithelium through which water and salts move across rapidly to maintain osmotic balance between the bowel contents and the blood. Diarrhea occurs when a poorly absorbed, osmotically active substance (usually a carbohydrate) is present in the gut lumen. The stooling stops on fasting, the stool pH is acidic and reducing substances are positive. Removal of the unabsorbed component of the diet is the only treatment. The unabsorbed substance is usually isosmotic and therefore dehydration and electrolyte disturbances are unlikely. Secretory diarrhea is caused by toxins [for example, cyclic AMP of cholera, cyclic GMP of enterotoxigenic *Escherichia coli* (ETEC)], which impair sodium absorption by the villus cells, while the chloride secretion by the crypt cells continues. The stooling continues despite fasting, the stool pH is alkaline and reducing substances are negative. Dehydration and electrolyte imbalances are common. Ion transport disorders (congenital chloride or sodium diarrhea) present with watery stools in the newborn period and result in failure to thrive and severe electrolyte disturbances. Increased gut motility from VIPoma, carcinoid or thyrotoxicosis are rare in children, but should be considered in chronic watery diarrhea when other causes are ruled out. Dysentery occurs from an inflammatory diarrhea and may be either infective (*Shigella*, *Salmonella*, amebiasis) or noninfective [inflammatory bowel disease (IBD), cow's milk protein allergy].

ABDOMINAL PAIN

Differentiating the varied types of functional abdominal pain from those with an organic pathology is a big challenge in practice. Pain-related functional GI disorders were categorized into five groups in the Rome III criteria of 2006: functional dyspepsia, irritable bowel syndrome, abdominal migraine, childhood functional abdominal

pain, and childhood functional abdominal pain syndromes. It is important however to recognize signs and symptoms that are suggestive of an underlying organic disease (**Table 1**).

Clinically, there are three patterns of abdominal pain in children: (1) Isolated per-umbilical pain, in which only 5% are organic causes (malrotation, renal stone, pelviureteric junction obstruction, food allergy); (2) upper abdominal pain with dyspepsia, in which 10% are organic [gastroesophageal reflux disease (GERD), *H. pylori*, pancreatitis, biliary disease and food intolerance] and (3) lower abdominal pain with altered bowel habits in which over 25% have an organic basis (constipation, IBD, lactose intolerance and gynecological). A careful history is important and helps avoid unnecessary investigations.

VOMITING

Vomiting, a complex protective reflex which helps rapid expulsion of any ingested toxins has three linked components: nausea, retching and emesis. It is a common symptom that occurs in many disease states, the cause of which is age-related. While congenital anomalies of the GI tract, necrotizing enterocolitis and inborn errors of metabolism are the most common causes in neonates, infections of the GI and hepatobiliary system, urinary tract and CNS as well as food allergy/intolerance predominate in infants and young children. In infants, it is important to distinguish reflux, which is the effortless passive bringing up of gastric contents, and involves no muscular activity. Gastroesophageal reflux is a physiological phenomenon that improves with age and most infants remain healthy. At any age, presence of any of the following features is very suggestive of an abdominal surgical cause: persistent vomiting with distended abdomen or constipation, bilious vomiting, absent bowel sounds, GI bleeding, point tenderness or diffuse guarding. Altered sensorium points to a CNS cause, electrolyte imbalance, liver/renal failure, diabetic ketoacidosis or poisoning.

In patients with recurrent episodes of vomiting, malrotation of gut, superior mesenteric artery syndrome, obstructive uropathy, chronic pancreatitis, diabetes, adrenal insufficiency, CNS lesions as well as inborn errors of metabolism should be considered. Cyclic vomiting syndrome is essentially a diagnosis of exclusion and is characterized by episodes of persistent vomiting without an identifiable cause, interspersed with complete symptom-free periods. The episodes may last up to 72 hours, cease spontaneously and often result in dehydration and electrolyte disturbances. Some have a family history of migraine and respond to antimigraine prophylaxis. The routine use of antiemetics in infants and children without a clear understanding of the underlying disease should be discouraged.

CONSTIPATION

Constipation is defined as delay or difficulty in defecation that causes significant distress to the child. If it persists more than two weeks, it is referred to as chronic constipation. Acute constipation is easier to treat and usually caused by a change in feeds, addition of formula in infants, sudden change in diet or place of stay, low-fiber diet, anal fissure or drugs. Chronic constipation is generally diet- and habit-related and presents a challenge in management.

Table 1 Features suggestive of an organic cause in chronic abdominal pain

• Localized or radiating pain	• Dysphagia
• Pain that wakes the child from sleep	• Persistent vomiting
• Gastrointestinal bleeding	• Malabsorption stool
• Growth deceleration or weight loss	• Unexplained fever
• Chronic GI disease in family	• Oral ulcer/perianal disease

Organic causes of chronic constipation are given in **Table 2**. While examination of the spine and the anal region is mandatory in all children with constipation, rectal examination should be avoided unless indicated. Associated urinary tract infection should be ruled out.

Encopresis is the involuntary passage of semiformed stool in a child's inner wear and is generally seen with functional constipation. Fecal incontinence is consistent fecal soiling and usually seen in association with an organic or anatomic lesion.

MALABSORPTION

Malabsorption is said to be present when there is a persistent disturbance of the digestive-absorptive process across the intestinal mucosa and is usually associated with growth faltering. The normal process of digestion involves three important steps: solubilization (fats by micelle formation), digestion (by specific digestive enzymes) and mucosal absorption (by diffusion or carrier-mediated transport). Maldigestion occurs when the amount of bile or pancreatic enzymes in the intestine is inadequate; for example, cholestasis and pancreatic insufficiency. Classical malabsorption occurs when there is a mucosal disease and defective absorption; for example, celiac disease, giardiasis and cow's milk protein allergy. The stools are pale, bulky with steatorrhea and foul smell in impaired fat digestion and explosive watery in defective carbohydrate digestion. In malabsorption, the child has flatulence and bloating; the stool contains both fat globules and fatty acid crystals, and there is associated anemia and hypoalbuminemia. In maldigestion, there is no bloating; the stool contains only fat globules and the child has no anemia or hypoalbuminemia.

GASTROINTESTINAL HEMORRHAGE

Upper GI bleeding defined as bleeding above the ligament of Treitz (esophagus, stomach and duodenum) presents with hematemesis. Only sudden massive bleeding causes bright red blood, since exposure to gastric juice quickly changes the color to coffee ground. While swallowed maternal blood and hemorrhagic disease are the most common cause in a well neonate, stress ulcer, coagulopathy and vascular anomaly should also be considered. In older children, esophagitis, gastric erosions and varices are relatively common, while prolapse gastropathy, Mallory-Weiss tear and vascular lesions are unusual causes. An upper GI endoscopy is the investigation of choice. A significant upper GI bleed can result in melena for three to five days.

Lower GI bleeding refers to bleeding beyond the ligament of Treitz and presents in two different ways:

1. Melena refers to black tarry stools, the black color being due to hematin, formed by the oxidation of haem by intestinal bacteria. Melena usually occurs when the bleeding is proximal to the ileocecal valve, but can occur in proximal colonic bleeds if the colonic transit time is slow.
2. Hematochezia is the presence of red blood in stool and is seen in colonic disease or in massive bleeds in the small intestine. Necrotizing enterocolitis, Hirschsprung enterocolitis and malrotation with volvulus are common causes in a neonate. While infectious enterocolitis, anal fissure and milk protein allergy are causes of mild bleeding in infants and young

children, Meckel's diverticulum and intussusception can cause massive blood loss. In older children, infectious colitis, polyp, hemorrhoids, IBD and Henoch-Schönlein purpura require consideration. Hematochezia limited to spots or streaks on the outside of the stool suggest an anorectal source. However, if it is mixed through the stool, it suggests a local pathology above the rectum and if it is seen with mucous in a loose stool, it is characteristic of colitis. Maroon-colored blood suggests significant bleeding in the distal small bowel and currant jelly stools are indicative of ischemic bowel lesion as in intussusception or volvulus. In melena, the more proximal the bleed, the darker black will be the stool.

ABDOMINAL DISTENSION

Abdominal distension is either due to a lax abdominal wall, a mass in the abdomen or from accumulation of fluid or gas within or outside the intestine. Ascites in significant amount distends the abdomen both anteriorly and in the flanks. The ascitic fluid is usually a transudate with low protein concentration and commonly results from increased portal venous pressure and/or reduced oncotic pressure from hypoalbuminemia. Portal hypertension per se is unlikely to cause clinically apparent ascites, until serum albumin declines. Exudative ascitic fluid has a high protein concentration and indicates an inflammatory pathology. When fluid or gas distends the gut, a mechanical or functional obstruction of the gut should be suspected. While gas filled loops of intestine will yield a tympanitic resonance over the periumbilical area, gas in the peritoneal cavity will result in a tympanitic resonance even over the solid organs like the liver. Localized abdominal distension can occur from enlargement of liver, spleen and kidney, a tumor or a congenital or acquired cyst.

IN A NUTSHELL

1. Watery stools indicate small bowel pathology, commonly of viral etiology.
2. Dysentery is diarrhea with visible blood in the stool and implies a large bowel disease.
3. Periumbilical episodic abdominal pain is functional in most children.
4. In children with persistent vomiting, intestinal surgical causes and extraintestinal medical causes should be considered.
5. Chronic constipation in young infants has an organic basis, while in older children, it is functional.
6. Hematemesis indicates bleeding above the ligament of Treitz and requires upper GI endoscopy.
7. Hematochezia occurs in distal colonic disease while melena suggests bleeding proximal to the ileocecal valve.

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Table 2 Organic causes of chronic constipation

Surgical	Medical
Local anal pathology	Drugs
Hirschsprung disease	Hypothyroidism
Anterior anus	Mental retardation, hypotonia
Spina bifida	Tethered cord
Meningomyelocele	Hypokalemia, hypercalcemia

Chapter 35.3

Cleft Lip and Cleft Palate

VS Akbar Sherif, Sayed Mohammed Akbar

Cleft lip (CL) and cleft palate (CP) are the most frequently encountered congenital anomalies of the craniofacial region. In India, about 30,000 babies with a cleft are born every year. The main categories of cleft are CL, CP, or CL and CP. They can present as an isolated anomaly, as part of a syndrome or associated with other anomalies.

Children affected with cleft will have a range of esthetic and functional problems, which leads to poor feeding, repeated ear and chest infections, malnutrition and even death in some cases. This situation has improved in recent times after the NGO—Smile Train began participating in surgical repair programs all over India. In 2008, WHO included CL and CP in the noncommunicable disease category in the Global Burden of Disease Initiative.

EPIDEMIOLOGY

The global prevalence of orofacial cleft is 1 in 700 livebirths. Males are more affected than females. Isolated CP is seen more in females. For reasons not known, left side is more affected than right. 75% clefts are unilateral and 25% bilateral. The risk for the next sibling getting affected is as follows:

- *Normal parents with one cleft child* 4% risk for the next child to have CL/CP
- *Normal parents with two kids with CL/CP* 9% risk for the next sibling
- *One parent affected with CL/CP, no affected kid* 4% risk for the next child
- *One parent and one child with CL/CP* 17% risk for the next child.

Siblings of babies with severe forms of CL/CP carry a high-risk of acquiring clefts. By high resolution ultrasonography, orbicularis oris muscle discontinuity has been demonstrated in relatives of patients with nonsyndromic clefts.

ETIOLOGY

The exact etiology is not known but is believed to be multifactorial involving both genetic and environmental factors. Although facial clefts occur in a variety of genetic syndromes, identification of a single gene controlling lip and palate cleft has not yet been identified. About 15% of the clefts are syndromic and more than 170 syndromes have cleft as a feature. Certain specific chromosomal aberrations are consistently seen, like trisomy D syndrome with midline cleft, 22q11.2 in velocardiofacial syndrome (CATCH 22). Few environmental factors are known to increase the incidence of clefting. They include factors like drugs (phenytoin, retinoic acid), maternal smoking, alcohol, folate deficiency and rubella infection in early pregnancy.

EMBRYOPATHOGENESIS

Craniofacial region develops through active migration of cells and the rearrangement of facial prominences and pharyngeal arches. Hence, this area is more vulnerable to many congenital birth defects. The special cells which contribute for the majority of skeletal and connective tissue of the craniofacial region are the pluripotent neural crest cells. Upper lip develops by the 4th week of embryonic life as five prominences arranged around the future mouth, the stomodaeum. They are the single frontonasal process (FNP), paired maxillary and mandibular processes. The maxillary

and mandibular processes originate from the 1st branchial arch. Fusion of maxillary and FNP completes the formation of upper lip (**Fig. 1**). The lower lip and the lower jaw are formed by the fusion of the two mandibular processes in the midline. Fusion of maxillary and mandibular processes will complete the formation of cheek and angle of mouth (**Fig. 2**).

The palate develops later around 7–8 weeks of intrauterine life. The two palatal process of maxilla meet with each other in the midline and also with the premaxilla anteriorly. Initially, the palatal processes are vertically oriented because of the presence of developing tongue in between it. As the oral cavity develops space, the tongue will fall back allowing the palatal process to move horizontally and fuse in the midline. Pathological states where the tongue is too big or the capacity of the oral cavity is small will result in a CP. Classical example is the Pierre-Robin syndrome (**Fig. 3**).

Failure of fusion between maxillary and medial nasal process results in classical cleft lip (**Fig. 4**). If the fusion defect is bilateral, it results in bilateral cleft lip (**Fig. 5**). The lip and palate develop separately which means it is possible for a baby to be born with only CL, only CP or a combination of both.

CLASSIFICATION

Numerous methods have been developed for recording cleft deformities but none of them are accepted universally due to limitations, inadequate description of deformity and varying complexities. There are four basic structures involved in CL/CP. They are nose, lip, primary and secondary palate. These basic structures may be involved completely or incompletely in many combinations. The morphological classification given below helps the clinician to understand the severity, grading, communication and treatment planning.

- *Isolated CL/CP* Unilateral/bilateral: Complete/incomplete
- *Combined CL/CP* Unilateral/bilateral: Complete/incomplete
- Syndromic.

CLINICAL PROBLEMS

Besides the obvious facial deformity from an external cleft, immediate functional concerns are for airway patency and the

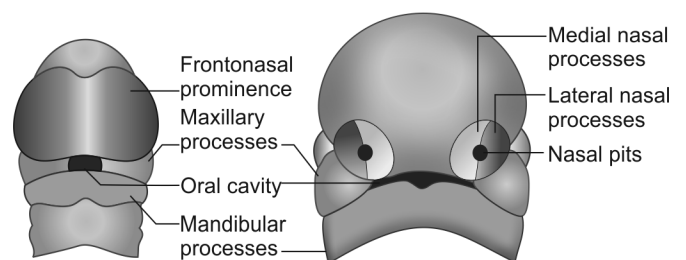


Figure 1 Formation of upper lip

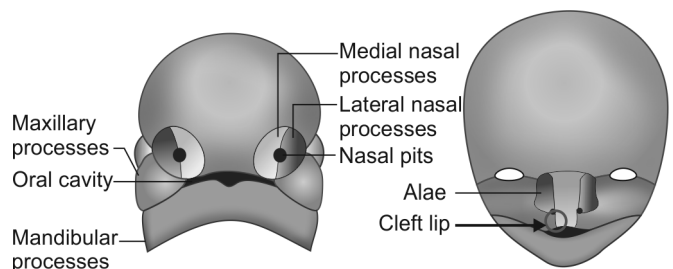


Figure 2 Formation of cheek and angle of mouth



Figure 3 Pierre-Robin syndrome. Note small and receding chin

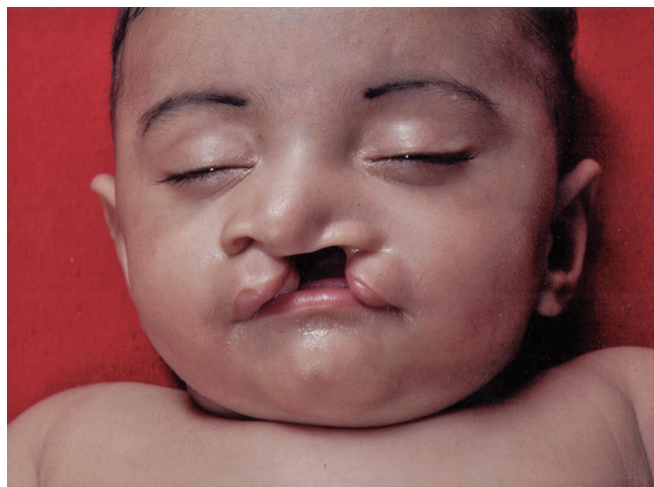


Figure 4 Unilateral cleft lip



Figure 5 Bilateral cleft lip

ability to feed. Certain clefts like the Pierre-Robin sequence will have severe life-threatening respiratory distress which may require immediate attention.

Feeding Problems

Normal feeding requires the creation of suction by velopharyngeal closure and compression by the orbicularis oris muscle and tongue. Babies with CL/CP cannot create a negative pressure for suction or compression. So, they may be given expressed breastmilk using special feeding devices or breastfed using feeding obturators. The baby should be fed every 2 hours, in a calm and quiet environment with the caregiver sitting in a comfortable chair. The teat should be kept on the uncleft side and gently squeezed after every 3–4 sucks. Feeding should not exceed to 20–30 minutes, since longer feeds are energy-consuming leading to poor weight gain. If bottle fed, the baby should be kept upright to prevent nasal regurgitation. Special teat or bottle which can be squeezed while the baby is sucking is now available. This will push the milk into baby's mouth and will compensate for suction.

Nasal Regurgitation and Aspiration

In babies with CL/CP sucking and swallowing mechanisms are defective, which leads to repeated aspiration pneumonia. Aggressive treatment may be needed to control the pneumonia. Feeding the baby with head-up position will decrease the problem until they learn adaptive techniques to overcome the handicap.

Middle Ear Infection

A majority of CP/CP patients develop middle ear infections, which if recurrent leads to conductive hearing loss. This predisposition may persist even after CP repair. The tensor palatini muscle is attached to the cartilaginous part of eustachian tube. Normally when this muscle contracts as in the act of swallowing or yawning, it will open up the eustachian tube equalizing the pressure in the middle ear and allowing drainage of any secretion. In babies with cleft palate, the action of this muscle is ineffective leading to fluid accumulation and infection. Also the eustachian tube is directly exposed in these babies, with regurgitation of milk feeds leading to edema and infection. Adenoid hypertrophy secondary to repeated infections also contributes to eustachian tube obstruction.

Speech Problems

The suction and compression of the breast during the normal feeding produces a coordination of these muscles, which is essential for normal speech development. This co-ordination is missing in children with cleft palate. The other factors which contribute to the poor speech development are velopharyngeal incompetence, palatal fistula, poor hearing, dental malocclusion and psychological factors. Hypernasality of speech is very common.

Psychosocial Problems

The facial appearance of babies with cleft interferes with early mother-child bonding. Patients with CL/CP show very low self-esteem and have difficulty in social interactions. Family environment is very important in rehabilitation of these children.

Dental Problems

Children with cleft may have special problems related to missing, malformed, malpositioned teeth. The first orthodontic evaluation is done before dental eruption and helps assess the facial growth, especially the growth of the jaws.

DIAGNOSIS

Craniofacial clefts can be diagnosed by antenatal ultrasonography, as early as 18–20 weeks of gestation. Antenatal diagnosis gives the family time for prenatal education, prenatal psychological preparation and counseling. After birth, minor forms of clefts like the forme fruste cleft lip or the submucosal cleft palate may

produce diagnostic confusion. Submucosal CP presents with nasal regurgitation, otitis media and poor speech. Examination will show a bifid uvula, midline of palate showing a pearly white line due to mucosal union alone. This will require treatment like any other CP.

MANAGEMENT

Considering the anatomical complexity of cleft, its effect on multiple orofacial functions, and its effect on orofacial growth and development, a multidisciplinary team approach is mandatory for optimal results. Prenatal diagnosis and parental interaction with the cleft team will lay the foundation for the subsequent surgical correction. After birth, attention should be given to ensuring the patency of airway, proper feeding advice and ruling out associated anomalies.

The goals of surgical treatment include repair of birth defect without affecting the growth of face, achieving normal speech, language and hearing, ensuring functional dental occlusion and dental health, optimizing psychological and developmental outcome, and facilitating ethically sound, family-centered sensitive care in a cost-effective manner. The currently recommended treatment schedule is as follows:

- *Birth* Initial assessment, presurgical evaluation and orthodontics
- *3–6 months* Primary lip repair
- *9–12 months* Palate repair (before speech develops)
- *2 years* Speech assessment
- *3–5 years* Lip revisions
- *8–9 years* Initial intervention orthodontics
- *10 years* Alveolar bone grafting
- *16 years* Nasal revision
- *17–20 years* Orthognathic surgery.

Surgical Repair

The many types of surgical repairs available emphasize the fact that each cleft is different. Every patient should be explained the number of surgeries they need including secondary corrections and alveolar bone grafting. CL is traditionally repaired before palate repair between 3 months and 6 months. The rule of 10 (10 g hemoglobin, 10 pounds weight and 10 weeks of age) is useful as an initial criteria for patient selection for surgery. Preoperative orthodontic care involves repositioning of the displaced dentoalveolar segments with various intraoral and extraoral orthodontic appliances, and this makes the surgical correction easier. The nasoalveolar molding device (NAM) is most commonly used.

The ideal technique for palatoplasty is the one which gives perfect speech without affecting maxillofacial growth and hearing. *The surgical steps are:* Closure of the defect, correction of abnormal position of muscle tensor palatini, reconstruction of muscle sling, push back of soft palate to improve velopharyngeal valve

mechanism during speech, minimum raw area to be left either in the oral or nasal surface and tension-free suturing. Grafting of the tooth bearing portion of the maxilla completes the primary repair sequence of the original cleft deformities. This procedure is usually done around 10 years of age.

Despite optimal primary repair, most patients require secondary revision of lip, nose or both. Common secondary corrections include scar revision, vermilion realignment, philtral lengthening, nasal base rotation or nasal tip cartilage correction. Most of this scar revisions are done between 2 years and 4 years to allow scar maturation to occur before the child enters the school. Septorhinoplasty reconstructions are done once they pass the growth phase. Hypernasality of speech with velopharyngeal incompetence is a common sequel of palate repair. Corrective pharyngoplasty is done after confirmation by nasal endoscopy and video fluoroscopy. Some patients may also require orthognathic surgery at around 20 years to correct the midfacial hypoplasia of maxilla, malocclusion and cross bite.

IN A NUTSHELL

1. The global prevalence of orofacial cleft is 1 in 700 livebirths. Males are more affected. Left side is more affected; only 25% clefts are bilateral.
2. The exact etiology is not known but is believed to be multifactorial involving both genetic and environmental factors.
3. There are four basic structures involved in cleft lip and cleft palate. They are nose, lip, primary and secondary palate.
4. Besides the obvious facial deformity from an external cleft, immediate functional concerns are for airway patency and the ability to feed.
5. The goals of surgical treatment include repair of birth defect without affecting the growth of face, achieving normal speech, language and hearing, ensuring functional dental occlusion and dental health, optimizing psychological and developmental outcome, and facilitating ethically sound, family-centered sensitive care in a cost-effective manner.

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Chapter 35.4

Dental Caries

Madhu S

Dental caries is considered to be the single most common chronic childhood disease. It is found to be more common than asthma in children. The disease is neither self-limiting nor amenable to treatment with antibiotics. Proper advice given at the right time often helps the child to remain caries free or at least limit the severity of the lesion. The pediatrician, often the first medical professional to see the child is in a unique position to influence the child and the parent. It is extremely important for the pediatrician to know the details regarding the causes and preventive strategies available for this very common childhood disease. The disease often regarded and neglected as dental disease has the potential to cause severe bacteremia leading to worsening of the existing systemic conditions.

EPIDEMIOLOGY

Dental caries is a disease that occurs in proportion to the state of civilization. The main factors implicated in increased dental caries are the production of sugar commercially and increased use of refined food. The incidence of caries is directly proportional to sugar intake. Studies in 20th century showed a high incidence of caries in USA and European countries, whereas it was low in developing countries in Africa. In developed countries, the incidence of caries is in the reversal phase at present due to the preventive strategies taken. However, it is actually increasing in the developing countries due to the increased use of refined food and poor oral hygiene. The incidence of caries is low in children whose parents have low incidence of caries. This could be due to lesser vertical transmission of cariogenic microorganisms or due to the resistant structure of enamel, and quantity and quality of salivary factors acquired from the parents. The role of dietary factors is well-known. A definite correlation is now established between soft drink usage and dental caries.

ETIOPATHOGENESIS

Currently, the term dental caries is used to describe the signs and symptoms of a localized chemical dissolution of the tooth surface caused by metabolic events taking place in the biofilm (dental plaque) covering the affected area. This occurs in an interplay between the tooth, saliva, diet, microorganism and time. The basic hydroxyapatite crystal is constantly modified during and after development of enamel. Two ions constantly involved in the replacement of lattice crystals are carbonate and fluoride. With carbonate ion inclusion, the crystal becomes weak and with fluoride ion, it becomes strong. Trace elements also decide the demineralization-remineralization potential (**Table 1**). Higher the salivary clearance rate, better the caries protective effect. Increased dental caries is seen in conditions involving hyposalivation or xerostomia (**Table 2**). Salivary enzymes, immunoglobulins and buffers contribute to its antibacterial property (**Table 3**).

Role of Sucrose

Probably among all the etiological factors, diet is the main factor which can be controlled by the child and parent. Sucrose is considered to be the arch rival of tooth. In the presence of cariogenic microorganism, mutans are produced from sucrose, which help to form adherent plaque on tooth which help *Streptococcus mutans* to form the initial colony on tooth surface. The habit of snacking in between meals by children has a direct link to dental caries.

Table 1 Trace elements in enamel and its effect on dental caries

Trace elements	Effect
Flourine, phosphorus	Cariostatic
Molybdenum, vanadium, copper, strontium, lithium, gold	Mildly cariostatic
Selenium, magnesium, cadmium, platinum, lead, silicon	Caries potentiating

Table 2 Medical conditions with xerostomia and medications increasing susceptibility to dental caries

Disease	Use of medicine
Sjögrens syndrome	Antihistaminics
Salivary gland malignancies	Narcotics
Diabetes mellitus	Antidepressants
Thyroid disorders	Antihypertensives

Table 3 Salivary antibacterial property

Enzymes	Immunoglobulins	Buffers
Lysozyme	SlgA	Bicarbonates
Lactoferrin	IgG	Salivary proteins
Lactoperoxidase	IgM	Phosphates

This is because more time is available for the bacteria to act. Sticky chocolates and bakery items eaten frequently by the child also lead to increased food retention and caries. The main organisms associated with dental caries are *Streptococcus mutans* group, Lactobacilli species, filamentous bacteria, *Veillonella* species and *Streptococcus* other than mutans group (**Fig. 1**).

TYPES OF DENTAL CARIES

Pit and fissure caries seen on the deep pits and fissures of occlusal surface of molars and premolars (**Fig. 2A**), and smooth surface caries seen on the proximal surfaces (**Fig. 2B**) are the two main types of caries. In children, nursing caries warrants special attention. It is a unique pattern of tooth destruction seen exclusively in primary dentition. Different studies show prevalence as high as 45% in India. It is due to prolonged improper night feeding. Children fall asleep while bottle feeding, and there is prolonged pooling of milk in the oral cavity. The lower anterior teeth are somewhat protected due to the physical presence and cleansing action of tongue (**Fig. 3**). Proper instruction to the parents can completely prevent or limit this condition (**Box 1**). Rampant caries, another type of early childhood caries, can affect both primary as well as permanent dentition. The usual contributory factors are a reduced salivary flow due to any disease state of salivary glands, children treated with tranquilizers, Sjögren syndrome, and genetic factors. Night feeding with milk or sugar-containing juices, nutritional deficiency, improper diet and emotional disturbances can all be contributory to this condition (**Fig. 4**).

BOX 1 Instructions to parents to prevent nursing caries

- Avoid feeding while sleeping after 1 year
- Oral cavity should be wiped clean with a cloth after each feed
- If child has the habit of sleeping with milk, discourage it
- Reduce the amount of sugar in the milk or juices gradually
- Encourage the child to drink warm water after each feed.

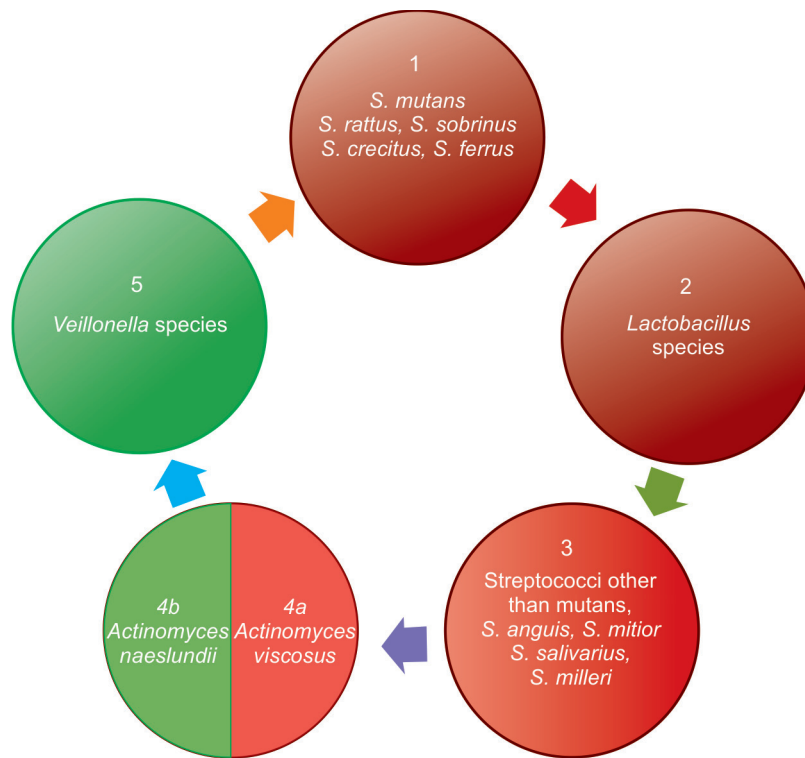
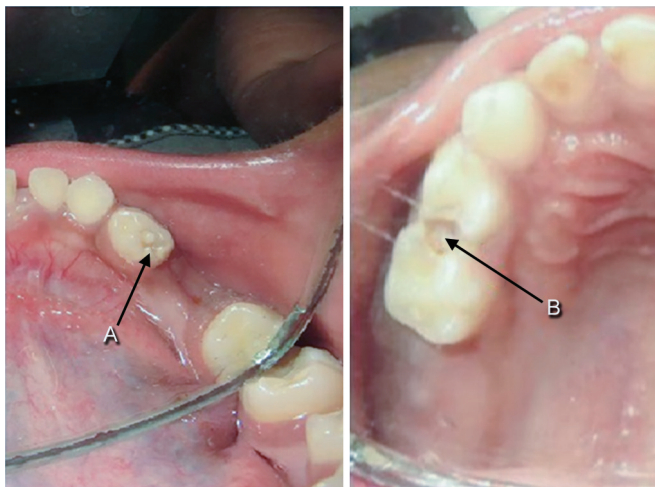


Figure 1 Microbiology of dental caries



Figures 2A and B (A) Pit and fissure caries; (B) Smooth surface caries



Figure 3 Nursing caries



Figure 4 Rampant caries

CLINICAL FEATURES

The common complaint with which the child is brought to a pediatric dentist is pain or swelling. Early sign detected is a white spot lesion. Here, the enamel surface is noncavitated but will become carious if demineralization continues. The child may have no pain in such lesions. Sensitivity and pain are features of the cavitated initial lesions. Deeper lesions show more pain and features of reversible pulpal damage. When infection progresses to affect the pulp, severe spontaneous and night pain will be present which suggests that pulp is irreversibly damaged. Infections crossing the root and spreading into bone can result in cellulitis and space infections (**Fig. 5**).

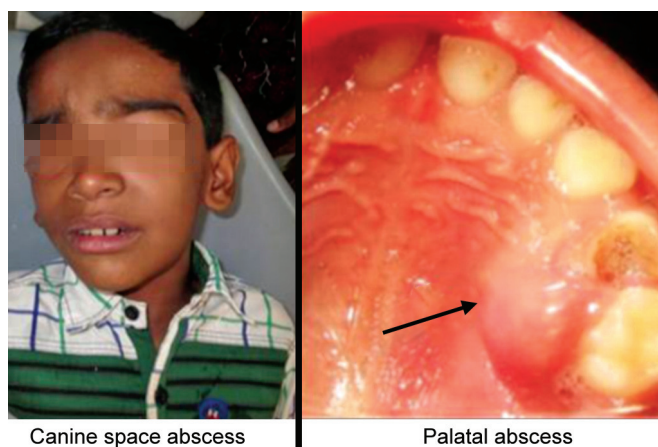


Figure 5 Space infection due to dental caries

APPROACH TO DIAGNOSIS

A major paradigm shift took place in the field of diagnosis of caries in 21st century. Earlier only cavitated lesions diagnosed with visual tactile examination were counted as decayed, whereas at present, even minimally demineralized lesions like white spot lesions detected with advanced diagnostic methods are counted as decayed.

MANAGEMENT

Early diagnosis of caries has resulted in two modes of treatment: nonoperative and operative. Nonoperative management is done in cases of early white spot and noncavitated lesions. This is done basically to arrest the progress of the lesion and to shift the environmental equilibrium toward remineralization so that more invasive operative treatment is avoided. The methods involved are maintenance of proper oral hygiene, use of antimicrobials, fluorides, remineralization agents and dietary control. Probably, the most important preventive method in early childhood caries (nursing or rampant caries) is dietary restriction. Instructions regarding feeding can be given to the mother (**Box 1**). Children's medicinal preparations for diseases like asthma, epilepsy, or fever are in syrup form with high sugar content. Vitamin supplements they regularly take at bedtime can be contributory to dental caries. Parents should

be informed about the effect the medicines can cause to the child's teeth and sufficiently motivated for the maintenance of oral hygiene after taking such medicines. Operative management involves use of different restorative materials. A lesion causing pulpal damage may have to be treated with endodontic treatment followed with a crown. Grossly decayed teeth may have to be extracted and a space maintainer provided to prevent space loss (**Fig. 6**).

CONCLUSION

A young child may often have a set of completely damaged teeth causing chronic severe pain so that he is unable to consume a proper diet resulting in malnutrition and even developmental delay due to lack of essential nutrients. Pediatricians, who are usually the first medical specialists to see such a child, are in a privileged position to give timely advice regarding feeding pattern and problems of night feeding (other than breastfeeding) which can go a long way in preventing debilitating childhood caries and associated problems.

IN A NUTSHELL

1. Dental caries is one of the most common chronic childhood diseases.
2. Dental caries, once established, always leaves a scar and can progress further leading to complications.
3. Many systemic diseases including cardiovascular diseases can get worse due to bacteremia from untreated lesions.
4. Night feeding (other than breastmilk) and its sequelae should be explained to the parents.
5. Pediatricians are often the first medical professionals to see a child, and in a position to give valuable suggestions to parents to prevent this dental disease.

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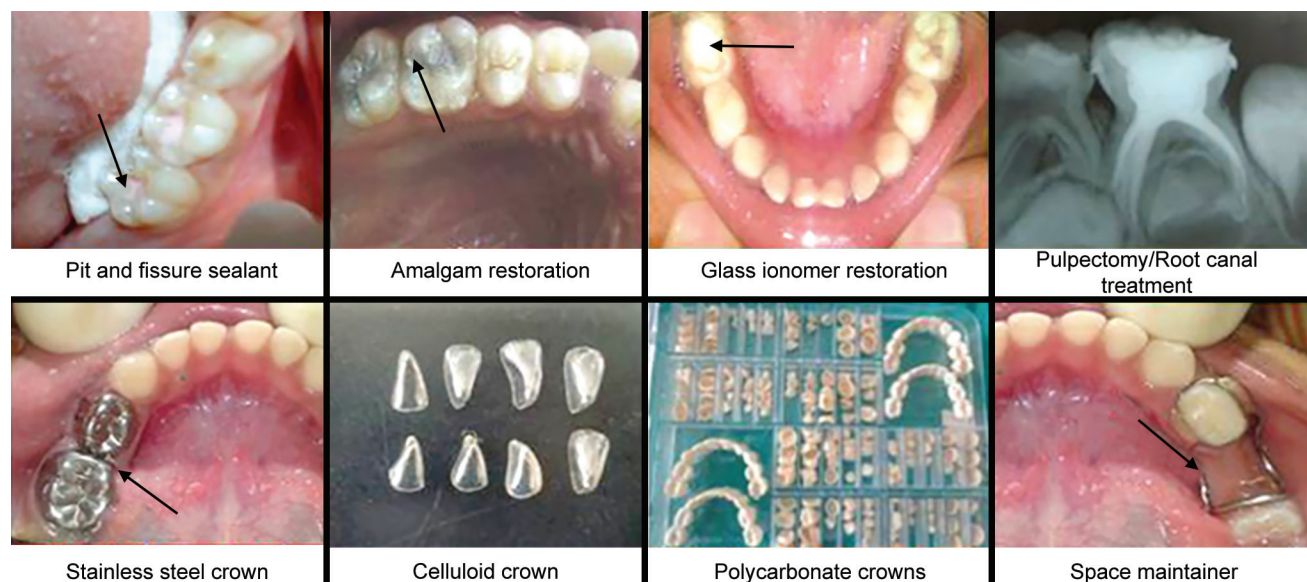


Figure 6 Operative treatment modalities for dental caries

Chapter 35.5

Recurrent Parotitis

Prakash Agarwal

Recurrent parotitis is defined as recurrent inflammation of one or both parotid glands. It is usually associated with swelling, pain, fever and redness. It is also known as juvenile recurrent parotitis or recurrent sialectatic parotitis. Recurrent parotitis is differentiated from suppurative parotitis by the inability to express pus from the parotid duct in recurrent parotitis.

EPIDEMIOLOGY

Recurrent parotitis has a male preponderance, and the peak age of onset is between 4 years and 6 years. Although rare, it is the most common inflammatory salivary gland disease in childhood after mumps. It presents with episodes lasting 4–7 days, approximately every 3–4 months. The disease is self-limiting usually resolves by adolescence, but a few cases may continue into adulthood. Mainly, the symptoms are seen to resolve after puberty.

ETIOLOGY

In vast majority of cases, its etiology is not known. Recurrent infection, allergy, congenital defects and genetic factors may play a role. Recurrent parotitis may be associated with Sjögren's disease and immune deficiency. As the age of onset increases, the diagnosis of Sjögren's disease is most likely. Certain viral infection like Epstein-Barr virus, parainfluenza virus, adenovirus, enterovirus, human herpes virus 6, enterovirus and parvovirus are implicated in recurrent parotitis. HIV-infected children are more prone to have persistent parotitis as part of the lymphoid interstitial pneumonitis complex. Recurrent parotitis may be associated with hypogammaglobulinemia, isolated IgG3 deficiency, and IgA deficiency. *Streptococcus viridans*, a mouth commensal, has also been implicated.

PATHOGENESIS

Its pathogenesis is still unknown. Decreased salivary flow may lead to stasis and cause damage to the ductules. The ductules may be abnormal from birth leading to inflammation and infection. Unilateral disease may be supported by pre-existing abnormality before the onset of clinical symptoms. Many asymptomatic glands had similar though often milder lesions. Most commonly mumps and other viral infections has been implicated but not proven to cause recurrent parotitis. According to Maynard, recurrent parotitis may be the end result of a sequence of events:

Initially, there is a low-grade inflammation of the gland and duct epithelium, due to low salivary flow rate due to dehydration and debility. This results in distortion and stricturing of the distal ducts, and metaplasia of the duct epithelium. The metaplasia results in excessive mucus secretion.

The histological picture includes lymphocytic infiltration around the intralobular ducts leading to damage of the duct wall reticulum, allowing extravasation of secretions into the gland parenchyma, and thus aggravating the inflammation.

CLINICAL FEATURES

It is characterized by intermittent swelling (**Fig. 1**) and redness of one or both parotid glands associated with pain, which can be very distressing. Overall condition of the patient may be good. The child



Figure 1 Parotid swelling

may have difficulty in mastication with coexisting fever. There may be signs of dehydration in severe parotitis. The saliva expressed from the Stensen's duct may be grainy and whitish compared to bacterial parotitis where it will be frank pus.

DIAGNOSIS

Suppurative bacterial parotitis, mumps, benign lymphoepithelial cysts and stone in the duct should be excluded. It is distinguished from suppurative bacterial parotitis by the absence of pus from the parotid duct.

Approach to Diagnosis

The diagnosis of recurrent parotitis is made on a clinical basis, and can often be confirmed by ultrasound, showing the classical features of sialectasis. Serum amylase may be elevated in acute parotitis. Sialogram may suggest multiple hypoechoic areas that correspond to the punctate pools. Histology may show periductal lymphocytic infiltration. Mutations of *SPINK-1* gene may predispose to juvenile parotitis. CT and MRI help to assess parotid tissue, along with MR sialography. Ultrasound scan has the advantage of being less invasive and can exclude stones, abscess and mass lesions. A normal ultrasound or sialogram does not exclude the condition. Sialendoscopy may be diagnostic and therapeutic. On scopy, the duct opening may be avascular and whitish compared to a normal opening, thereby confirming the diagnosis.

MANAGEMENT

Treatment may range from conservative measures to radiotherapy and total parotidectomy as in the past. As it is a relatively benign condition, conservative symptomatic treatment is recommended. Majority of the cases are viral in origin, and hence the role of antibiotics is doubtful. Nonsteroidal anti-inflammatory drugs (NSAIDs) are given to control pain and rarely fever. Sialogogic agents, warmth and massage and duct probing have been recommended. Ductal irrigation and dilatation may be possible by sialendoscopy. It gives a correct picture of the duct opening which is whitish and avascular compared to a normal duct. Intraductal irrigation with intraglandular hydrocortisone may give some relief. Surgical options are total parotidectomy in resistant cases, which is curative, but carries with it the inherent risks of nerve damage. Stensen's duct ligation with tympanic neurectomy may give some relief.

IN A NUTSHELL

1. Recurrent parotitis is presents with swelling, pain, fever and redness of parotid glands lasting 4–7 days, approximately every 3–4 months. It is also known as juvenile recurrent parotitis.
2. Recurrent parotitis is differentiated from suppurative parotitis by the inability to express pus from the parotid duct in recurrent parotitis.
3. Recurrent parotitis has a male preponderance, and the peak age of onset is between 4 years and 6 years.
4. Recurrent infection, allergy, congenital defects and genetic factors may play a role. Recurrent parotitis may be associated with Sjögren's disease and immune deficiency.
5. The disease is self-limiting, usually resolves by adolescence, but a few cases may continue into adulthood.

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Chapter 35.6

Vomiting

Sumathi Bavanandam

Vomiting is a common problem in children and can occur in diseases involving many organ systems. Causes of vomiting vary from respiratory tract infection to more serious conditions like inborn errors of metabolism, central nervous tumors apart from gastrointestinal (GI) disease. A good history and thorough physical examination are important in identifying the underlying etiology and tailoring the investigations. Any child with prolonged vomiting (> 12 hours in a neonate, > 24 hours in children younger than two years of age, or > 48 hours in older children) should undergo appropriate investigations.

DEFINITIONS

- **Vomiting** Is an active process and involves the forceful expulsion of gastric contents through the mouth associated with contraction of the abdominal and chest wall musculature.
- **Regurgitation** Is a passive process in which food from the stomach is brought back into the mouth without abdominal and diaphragmatic muscular activity.
- **Rumination** This is a chewing and swallowing process of regurgitated food that has come back into the mouth which occurs within minutes of eating (or even during eating), through a voluntary increase in abdominal pressure.
- **Recurrent vomiting** At least three episodes of vomiting in a three-month period which may be chronic or cyclical.
- **Acute vomiting** Abrupt onset of short-term vomiting.
- **Cyclical vomiting syndrome (CVS)** Characterized by recurrent, discrete, self-limited episodes of vomiting and is defined by symptom-based criteria with negative laboratory, radiographic and endoscopic testing.
- **Psychogenic vomiting** There is no underlying organic cause. It is often chronic and is due to cortical or psychological input. Stressful events precipitate an attack and many children require hospitalization.

PATHOPHYSIOLOGY

The act of vomiting is a complex, coordinated autonomic response triggered by peripheral and central stimuli and involves neural, hormonal, and muscular responses generated by the reticular formation of the medulla with its several scattered groups of neurons. The vomiting center is located in the lateral medullary reticular formation of the brainstem and is the final pathway. The center has predominantly muscarinic (M1), histamine 1 (H1), neurokinin 1, and serotonin receptors and receives input from four distinct centers, namely chemoreceptor trigger zone, vagal afferent system, vestibular system and high cortical centers. Area postrema situated in medulla contains predominant D2 dopamine receptors and is unprotected by blood-brain barrier. As a result of this sampling of peripheral blood and cerebrospinal fluid, various metabolic and hormonal disorders can cause vomiting. Luminal distension or irritation of GI mucosa from various causes result in activation of vagal afferent system (mediated by serotonin receptors) and cause vomiting. In motion sickness and labyrinthine disorders, the vestibular system mediated via M1- and H1-receptors is involved in pathogenesis of vomiting.

The phases of vomiting are pre-ejection phase, a retching phase, and ejection phase. There is gastric relaxation and retrograde peristalsis in pre-ejection phase. During the phase of retching, there

is rhythmic contraction of respiratory, abdominal wall, intercostal, and diaphragm muscles against a closed glottis. In the final phase of ejection, there is intense contraction of the abdominal muscles along with relaxation of the pharyngoesophageal sphincter. These sequential events are not seen in projectile vomiting as in gastric outlet obstruction.

DIFFERENTIAL DIAGNOSIS

Vomiting is a symptom with a wide differential diagnosis, ranging from lesions of the GI tract to systemic illnesses, metabolic, endocrine, central nervous disorders to rare inborn errors of metabolism. Acute onset of vomiting with severe abdominal pain may suggest a surgical origin and is usually associated with localized or generalized abdominal tenderness, rigidity, absent or hyperactive bowel sounds. Causes of vomiting based on age are illustrated in **Table 1**. **Table 2** shows the *red flag signs* of vomiting.

EVALUATION

A detailed history, including diet, drug intake, family history, surgical history is important in the initial evaluation to identify a cause. History should include the following:

- Onset and type, whether acute, chronic or episodic
- Presence of nausea, headache, visual disturbances, photophobia, suggestive of migraine
- Previous history of surgery indicating adhesive obstruction
- Projectile vomiting without nausea suggestive of central nervous system (CNS) pathology
- Bilious vomiting to indicate a possible surgical cause (though it can occur in nonsurgical conditions)
- Presence of blood in the vomitus due to mucosal ulcerations, erosions or variceal bleed
- Feculent vomitus to indicate intestinal/colonic obstruction or gastrocolic fistula
- Presence of abdominal pain, food-related pain indicating peptic ulcer disease
- Stale food vomitus in gastric outlet obstruction
- Undigested food often seen in achalasia cardia, Zenker's diverticulum.

Physical Examination

Physical examination should focus on the following: Assessment of nutritional status, growth and development, assessment of hydration status, presence of anemia, icterus, abnormal odor, and abnormal neurological signs. Abdominal examination should include abdominal tenderness, absent or exaggerated bowel sounds, scars, hernia orifices. Presence of visible gastric peristalsis indicates gastric outlet obstruction. Complications of persistent vomiting include dehydration, electrolyte disturbances, acid-base imbalance and nutritional deficiency.

Investigations

These are indicated for: (1) bilious vomiting, abdominal tenderness and/or severe abdominal pain; (2) attacks precipitated by intercurrent illness, fasting, and/or high protein meal; (3) abnormalities on neurological examination including severe alteration of mental status, abnormal eye movements, papilledema, motor asymmetry, and/or gait abnormality (ataxia); and (4) progressively worsening episodes or conversion to a continuous or chronic pattern.

Tests include complete hemogram, liver function tests, renal functional tests, blood sugar, urine ketones to rule out diabetic ketosis, urine routine and culture, lactate, electrolytes, ammonia, ketones and arterial blood gas analysis for inborn errors of metabolism. A plain abdominal X-ray is useful to rule out

Table 1 Common causes of vomiting depending on age

Neonate (< 1 month)	Infant (> 1 – 12 months)	Toddler (> 1 – 4 years)	Child (4 – 12 years)	Teenager (13 – 19 years)
GER and GERD Feeding intolerance, pyloric stenosis, meconium ileus, malrotation with midgut volvulus, necrotizing enterocolitis, congenital atresia/webs, metabolic disorders, Hirschsprung disease, protein intolerance infection (UTI/meningitis)	GER or GERD Acute otitis media, protein intolerance, UTI, acute gastroenteritis, malrotation, volvulus, meningitis, CNS tumors, intussusception, metabolic disorders	Urinary tract infection, pharyngitis, GERD, celiac disease, intracranial lesion, malrotation, poisoning	Gastroenteritis, pharyngitis, postinfectious appendicitis, celiac disease, pancreatitis, IBD, poisoning/toxic ingestion Eosinophilic esophagitis	Gastroenteritis, peptic ulcer disease, cyclic vomiting, eosinophilic esophagitis, pregnancy, poisoning/toxic ingestion, migraine, diabetic ketoacidosis, drug abuse, appendicitis, gallstone, pancreatitis, bulimia, IBD

Abbreviations: GER, gastroesophageal reflux; GERD, gastroesophageal reflux disease; UTI, urinary tract infection; IBD, inflammatory bowel disease; CNS, central nervous system.

Table 2 Red flag signs with probable causes of vomiting

S. No.	Vomiting characteristics/associated features	Probable cause
1.	Failure to thrive or weight loss	GERD, obstructive GI diseases, metabolic causes, urinary causes
2.	Projectile vomiting, presence of abnormal neurological signs	CNS tumors, meningitis
3.	Localized abdominal pain: Right upper quadrant pain— Localized epigastric pain	Gallbladder disease esophagitis, peptic ulcer
4.	Hematemesis/melena	Esophagitis, esophageal ulcer, peptic ulcer, portal hypertension
5.	Severe dehydration with dyselektrolytemia	Serious underlying conditions, such as obstruction, CAH
6.	Bilious vomiting	Surgical causes Intestinal obstruction
7.	Short stature, anemia	Inflammatory bowel disease, hypothyroidism, or celiac disease
8.	Nocturnal vomiting, recurrent wheeze	Gastroesophageal reflux disease or postnasal drainage
9.	Fever, toxemia in young	Sepsis, meningitis
10.	Episodic vomiting with symptom-free interval	Cyclical vomiting syndrome

Abbreviations: GERD, gastroesophageal reflux disease; CAH, congenital adrenal hyperplasia; GI, gastrointestinal; CNS, central nervous system.

intestinal obstruction (**Fig. 1**); ultrasonography (USG) abdomen helps in diagnosis of hypertrophic pyloric stenosis, malrotation, intussusception, and obstructive uropathy. Barium contrast studies may be useful in gastroesophageal reflux disease (GERD), congenital esophageal stenosis (**Fig. 2**), achalasia cardia (**Fig. 3**), infantile hypertrophic pyloric stenosis (IHPS), duodenal web/atresia and intestinal narrowing. Upper GI endoscopy is useful in diagnosis of mucosal disease of upper GI tract (**Fig. 4**), *H. pylori* gastritis, eosinophilic esophagitis, and obstructive causes like strictures. Esophageal manometry helps in achalasia cardia and motility disorders of esophagus. CT brain/MRI is useful for identifying CNS tumors.

TREATMENT

Treatment depends on the underlying cause. A course of proton pump inhibitor (PPI) or histamine 2 receptor antagonist (H2RA) will benefit children with GERD. Avoidance of cow milk, thickening of feeds, and positioning will be of benefit. Infants and young children outgrow the problem by 1–2 years. Treatment options for eosinophilic esophagitis include acid suppression, corticosteroids (topical and systemic), and dietary modifications like elimination diet, like milk, soy, egg, peanut, wheat and fish or complete elemental diet. Stricture of esophagus secondary to eosinophilic esophagitis needs cautious endoscopic dilatation. Swallowed fluticasone (44–220 mg per swallowed puff) given as two puffs two times a day has been effective. Endoscopic stricture dilatation may be needed for peptic, corrosive and anastomotic strictures. Surgical management is indicated in IHPS/malrotation/intestinal atresia/web and intestinal obstruction. The recommended indications

of antiemetics are chemotherapy/radiation-induced vomiting, postoperative vomiting, cyclical vomiting and vomiting due to GI motility disorders.

CYCLICAL VOMITING SYNDROME

The exact etiology and pathogenesis of cyclical vomiting syndrome (CVS) still remain unclear. Girls are affected more than boys. Migraine variant, mitochondrial fatty acid oxidation disorders, GI motility disorder, disorder of the brain-gut axis, autonomic dysfunction, abdominal epilepsy, ion channel dysfunction, corticotropin-releasing factor in response to stress, altered psychodynamics, mitochondrial energy depletion due to mitochondrial mutation precipitated by stress/excitement are some of the proposed mechanisms that can trigger episodes of vomiting in children with CVS. The bilious vomiting is intense associated with disabling nausea and dehydration requiring hospitalization. Accompanying symptoms including pallor, listlessness, anorexia, nausea, retching, abdominal pain, headache and photophobia may make it difficult to distinguish episodes of CVS from other causes of acute abdomen and altered consciousness. Migraine, motion sickness, epilepsy, anxiety and depression are some of other observed associations of CVS. There are no specific laboratory markers to diagnose CVS. Since vomiting is often bilious and associated with pain, investigations need to be done to exclude organic causes.

Criteria for Diagnosis

- At least five attacks in any interval, or a minimum of three attacks during a 6-month period



Figure 1 Plain abdominal X-ray with multiple air fluid level in intestinal obstruction

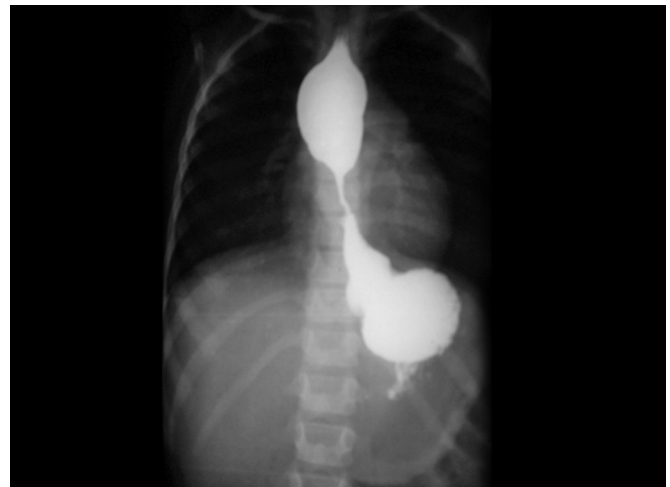


Figure 2 Barium swallow showing long segment narrowing—congenital esophageal stenosis



Figure 3 Barium swallow in an infant showing dilated esophagus with smooth distal tapering suggestive of achalasia cardia

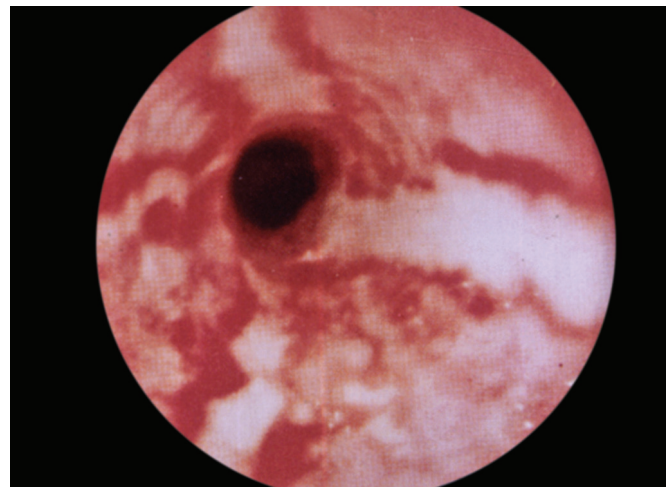


Figure 4 Upper gastrointestinal endoscopy showing severe esophagitis

- Episodic attacks of intense nausea and vomiting lasting 1 hour–10 days, occurring at least 1 week apart
- Stereotypical pattern and symptoms in the individual patient
- Vomiting during attacks occurs at least 4 times/hour for at least 1 hour
- Return to baseline health between episodes and not attributed to another disorder.

Treatment

During an acute attack, taking care of hydration and electrolytes is essential to prevent dehydration as well as in decreasing the duration of the acute illness. Ondansetron provides symptomatic relief. Sedation is usually beneficial during the episode. Avoidance of triggers such as fasting, intake of caffeine, chocolates are essential to avoid an attack. If the attack is more than one per month, prophylactic drug therapy is advisable. Propranolol has

been recommended as first-line prophylactic drug with good response in more than 85% of patients. Tricyclic antidepressants are effective in 68% of children with CVS. Phenobarbital, topiramate, and sumatriptan are other drugs that can be tried.

ABDOMINAL MIGRAINE

Abdominal migraine is defined as attacks of abdominal pain lasting for 1–72 hours, periumbilical or poorly localized, dull aching pain of varying intensity, usually accompanied with at least two of the following symptoms, namely anorexia, nausea, vomiting, and pallor. Thirty to forty percent of children can have associated headache. Family history of migraine can be documented in a subset of children. Vascular constriction causing ischemia of GI tract or CNS areas innervating the gut may be the cause. Clinical history, physical examination and investigations are essentially normal. Prophylactic use of propranolol can be useful.

IN A NUTSHELL

1. Vomiting is a symptom of a variety of disorders ranging from self-limited diseases to life-threatening diseases, and the treatment depends on the etiology apart from symptomatic therapy.
2. Good history and thorough physical examination are crucial to early identification of serious conditions.
3. Copious bilious emesis at any age is a sign of intestinal obstruction until proven otherwise.
4. Cyclical vomiting is not an uncommon cause of chronic recurrent episodic vomiting in older children and adolescents.
5. Presence of *red flag* signs and symptoms requires thorough evaluation and urgent attention.

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Chapter 35.7

Infantile Hypertrophic Pyloric Stenosis

Ketan Parikh

It is characterized by persistent nonbilious vomiting in a neonate and may lead to significant dehydration and metabolic disturbances if not diagnosed early enough. It was earlier believed that the condition is relatively rare in India; however, a relatively higher incidence is being reported in recent times. Most cases are sporadic but few cases may run in families. Boys (mostly first-born) are five times more commonly affected than girls.

PATHOLOGY

Musculature of the pyloric antrum is significantly hypertrophied, thus the pylorus is thickened and the pyloric canal is lengthened and narrowed. The hypertrophied pyloric muscle becomes olive-shaped and becomes hard to feel when contracted. This hypertrophied pylorus is clinically palpable as a 'pyloric tumor'. The stomach proximal to the obstruction is dilated and is also secondarily hypertrophied.

Gastric mucosa in infancy produces a potent lipase which hydrolyses milk to free fatty acids. The hypertrophied pyloric muscle leads to a partial obstruction to the outflow from the pylorus. Thus there is stagnation of milk in the stomach. Rancidity of the curdled milk gradually causes progressive mucosal edema and precipitates complete obstruction of the narrowed and hypertrophied pyloric canal (**Fig. 1**) and thus symptoms are often delayed till 3–6 weeks.

CLINICAL FEATURES

Usually the child presents between 3 weeks and 6 weeks but the child may present anytime from 1 week to 4 months. Progressive, forcible, projectile and nonbilious vomiting is the most important presenting symptom. The vomitus may contain altered blood. The baby is usually very hungry after vomiting. There is associated weight loss or failure to gain weight. Constipation occurs due to poor intake. Jaundice is occasionally seen due to nutritional deficiencies. Facies is characteristic—alert, anxious and hungry look. These patients have a slow and shallow breathing due to the metabolic alkalosis secondary to persistent vomiting. Examination is characterized by visible gastric peristalsis on inspection (left to right) (**Fig. 2**). Examination must be done with the child comfortably placed in the mother's lap and in good light. Palpation of the "tumor" (palpable in 70% cases) is the diagnostic sign. It should be sought for with the left hand, sitting on the patients' left palpating below the right costal margin, below the liver border.

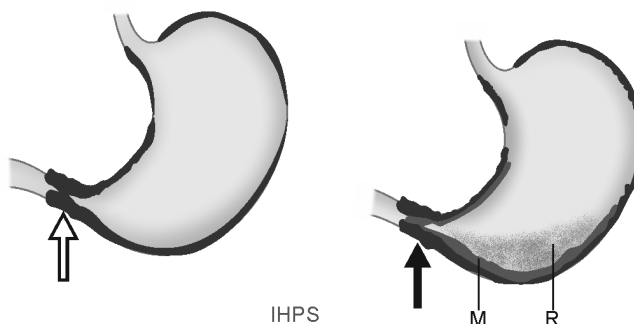


Figure 1 Pyloric muscle thickening (hollow arrow) causing partial obstruction and residue (R), causing mucosal edema (M) and resultant complete obstruction (block arrow)

DIAGNOSIS

Infantile hypertrophic pyloric stenosis (IHPS) needs to be differentiated from other causes of nonbilious vomiting in young infants: gastroenteritis; septicemia, meningitis, intracranial hemorrhage; gastroesophageal reflux, and achalasia cardia. USG shows the thickened pylorus and may also show reverse peristalsis on the stomach. Contrast studies with Barium (only if necessary) reveal a large stomach, delayed emptying, string sign, and gastritis (**Fig. 3**). Serum electrolytes and blood gas reveal hypokalemic hypochloremic alkalosis.

TREATMENT

Surgery is the treatment of choice. Nonsurgical treatment with prokinetics should be tried only in case of strong contraindication to surgery as the treatment has erratic results, is too prolonged and may lead to aspiration and malnutrition.

Preoperative correction of metabolic disturbances is an integral part of the surgical treatment and usually is achieved within 24 hours. Aggressive resuscitation can produce rapid fluid and electrolyte shifts, possibly leading to seizures. Correct dehydration and electrolyte imbalance. Aspiration of the gastric contents may help in reducing the gastric mucosal edema. If necessary a gastric lavage with normal saline would help. Oral rehydration with 0.33% or 0.5% dextrose saline with 20–40 mEq/L



Figure 2 Visible peristalsis (L → R) seen in a quiet child after feeding



Figure 3 String sign on upper gastrointestinal (GI) series

of potassium may help once the mucosal edema regresses within a few hours and this avoids the possible complications of rapid IV rehydration. Alternatively IV rehydration with 0.33% saline and appropriate potassium correction may be resorted to. Fredet-Ramstedt's pyloromyotomy is the desired procedure; which can be achieved by open or laparoscopic (**Fig. 4**) approach. The results are excellent with a low incidence of complications.

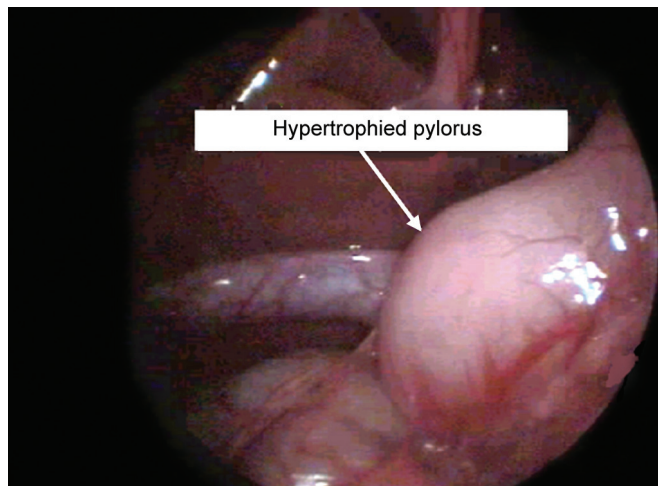


Figure 4 Laparoscopic view of hypertrophied pylorus, maybe palpable like an olive

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IN A NUTSHELL

1. IHPS should be suspected in any infant with persistent non-bilious vomiting.
2. Presence of visible gastric peristalsis (left to right) should increase this suspicion.
3. Ultrasonography is now the investigation of choice in the diagnosis of IHPS.
4. Serum electrolytes and blood gas reveal hypokalemic hypochloremic alkalosis.
5. Fredet-Ramstedt's pyloromyotomy is the desired treatment of choice.

Chapter 35.8

Gastroesophageal Reflux

Elsie Jazmin Foglio, Dinesh S Pashankar

Gastroesophageal reflux (GER) is one of the most common disorders of the esophagus in the pediatric age group. It can be defined as spontaneous and effortless passage of gastric contents from the stomach into the esophagus. GER may be physiological as seen in infancy or pathological. Gastroesophageal reflux disease (GERD) usually implies the presence of significant clinical symptoms due to pathological reflux and complications.

EPIDEMIOLOGY

Gastroesophageal reflux is common in infancy worldwide and usually presents as vomiting or regurgitation. In a population-based study involving 602 infants from New Delhi, the prevalence of regurgitation was noted to be 55% in infants between 1 month and 6 months of age and the prevalence dropped to 15% in infants between 7 months and 12 months. The prevalence of GER decreases with age in children, but increases again in adolescence. In a study from USA, symptoms of reflux in the form of heartburn and regurgitation were reported in about 2% of 3–9-year-old children and about 5–8% of 10–17-year-old children.

There are certain groups of children who are at high-risk for severe reflux and GERD. These include children with neurological impairment such as cerebral palsy and children who have had surgery for esophageal atresia. Obesity, presence of hiatal hernia, and chronic respiratory disorders are also predisposing factors for severe GER in children.

PATHOPHYSIOLOGY

Transient relaxation of the lower esophageal sphincter (TRLES) is defined as abrupt, prolonged (> 10 sec) and complete relaxation of the lower esophageal sphincter (LES). It occurs independent of swallowing and is the most frequent mechanism causing GER in children and adults. This inappropriate relaxation of LES tone allows gastric contents to enter the esophagus, thus exposing the esophageal mucosa to the acidic gastric contents.

Recurrent acid reflux can injure the distal esophageal mucosa resulting in esophagitis. Chronic esophagitis may lead to complications such as stricture or Barrett's esophagus, which may subsequently result in adenocarcinoma of esophagus. Fortunately, this complication is very rare in children. GER can cause respiratory complications either due to aspiration or reflex bronchospasm. Reflux of acid into the larynx may cause irritation leading to laryngitis or apnea.

CLINICAL FEATURES

Gastroesophageal reflux in infancy is physiological and presents as regurgitation or spitting. Weight gain is excellent and there is no evidence of complications such as esophagitis or respiratory symptoms. These infants are aptly called "happy spitters". The physiological reflux of infancy generally begins in the first few weeks of life, peaks at about 6 months and usually resolves by 8–12 months of age.

As opposed to physiologic reflux of infancy, GER in older children can be significant and lead to GERD. **Table 1** shows symptoms and the spectrum of complications of GER. Esophagitis is one of the most common complications of GER in children and usually presents with epigastric pain or hematemesis.

However, irritability with feeds or feeding refusal may be the only manifestation of esophagitis in younger children or neurologically impaired patients. Reflux esophagitis is being diagnosed more frequently in Indian children with the use of endoscopy. In a study from Lucknow, reflux esophagitis was diagnosed in 26 of 33 children who presented with symptoms suggestive of reflux. In the same study, other complications of reflux such as esophageal stricture, Barrett's esophagus and respiratory symptoms were also observed in Indian children.

There are a number of studies reporting an association between reflux and upper and lower respiratory symptoms in children. However, a clear etiologic role of reflux causing dental, ear, nose, throat and respiratory complications is not confirmed. The clinical association of bronchial asthma and GERD is well known although convincing causal relationship has not been established. *Waterbrash*, the sudden appearance of sour salty fluid in the mouth secondary to hypersecretion of the salivary glands in response to the presence of acid in the esophagus, may be seen in older children with GER. Some infants with severe GERD may present with failure to thrive secondary to frequent copious vomiting, and refusal of food due to the pain of esophagitis. Apnea in infants due to laryngospasm caused by nasopharyngeal microaspiration, and sudden infant death syndrome (SIDS) may be manifestations of GERD.

Sandifer syndrome is a rare complication of GERD. It is an unusual movement disorder characterized by spasmodic torsional dystonia with arching of the back and opisthotonic posturing. Hence, it may be mistaken for seizure disorder.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis of chronic vomiting is wide and is discussed elsewhere in this book. In young infants with severe vomiting, pyloric stenosis and malrotation should be considered and ruled out. In older children, acid peptic diseases such as gastritis or ulcer can present with vomiting and epigastric pain. Eosinophilic esophagitis, a condition more common in the Western World, can present with vomiting, epigastric pain and dysphagia. Neurological causes should be considered in children presenting with chronic vomiting and headaches.

APPROACH TO DIAGNOSIS

The diagnosis of GER can be made in many children based on history and physical examination. Particularly, a detailed history is all that is necessary to diagnose physiological reflux of infancy. In a growing infant who is otherwise well, daily vomiting of small volume is suggestive of physiologic reflux and no further investigations are necessary. The diagnostic criteria of infant regurgitation according to Rome III classification include regurgitation of two or more times per day for 3 or more weeks in otherwise healthy infants (3 weeks to 12 months of age) without retching, hematemesis, aspiration, apnea, failure to thrive, feeding or swallowing difficulties, or abnormal posturing. Infant questionnaire developed by Orenstein et al. has 11 questions which can be used to differentiate GER from GERD with high sensitivity and specificity (74% and 94%) in USA. However, when applied to Indian infants, this questionnaire had low sensitivity and specificity (43% and 79%) and has low diagnostic utility.

In older children, heartburn and regurgitation are the usual symptoms of GER. A careful history should be obtained to assess for GER and complications as shown in **Table 1**. It is important to determine the presence of predisposing risk factors, as mentioned above, as these children are likely to have severe reflux disease and require investigations and long-term therapy.

There are various diagnostic studies to assess reflux and complications and are shown in **Table 2**. There is no single test to assess GER in children and tests should be planned depending

Table 1 Symptoms and complications of gastroesophageal reflux

<i>Reflux</i>	<i>Lower respiratory tract*</i>
Vomiting	Bronchospasm, wheeze
Regurgitation	Chronic cough
Heartburn	Recurrent pneumonia
<i>Esophagitis</i>	<i>Upper respiratory tract *</i>
Feeding refusal, irritability	Laryngitis, hoarseness
Heartburn, epigastric pain	Obstructive apnea
Hematemesis	Dental erosions
Anemia	Sinusitis
<i>Esophageal stricture</i>	<i>Neurological</i>
Dysphagia	Sandifer's syndrome

* Possible association.

Table 2 Diagnostic studies for GER and complications

<i>Tests</i>	<i>Diagnostic utility</i>
Upper gastrointestinal series	<ul style="list-style-type: none"> To assess anatomical abnormalities To rule out malrotation, hiatal hernia, stricture
24-hour esophageal pH study	<ul style="list-style-type: none"> To detect acid reflux in the esophagus To correlate acid reflux and extraesophageal manifestations
Endoscopy with histology	<ul style="list-style-type: none"> To diagnose esophagitis, Barrett's esophagus To rule out gastritis, peptic ulcer, eosinophilic esophagitis To dilate esophageal stricture
Impedance study	<ul style="list-style-type: none"> To detect acid and nonacid reflux in the esophagus To correlate acid and nonacid reflux and extraesophageal manifestations

on the clinical presentation of the child. Upper gastrointestinal barium study is not a good test to diagnose reflux because of poor sensitivity and specificity, but it is useful to rule out anatomical abnormalities. Twenty-four hour esophageal pH study is useful to assess acid reflux in the esophagus. The test is performed by the transnasal placement of a standardized microelectrode into the lower esophagus, for continuous measurement and recording of intraesophageal pH for 24 hours. An episode of acid reflux is usually defined as an esophageal pH less than 4. Computerized analysis calculates the number, duration of reflux episodes and reflux index. The reflux index (percentage of time esophageal pH is less than 4) of more than 5% and 10% are suggestive of GER in children and infants respectively. The pH study is particularly useful to look for acid reflux in children with extraesophageal symptoms and to assess adequacy of acid suppression. Multichannel Intraluminal Impedance (MII) is a procedure that measures change in electrical resistance (impedance) between multiple electrodes located on an esophageal catheter. It is done with pH monitoring and can detect acid and nonacid reflux. MII can be useful for correlation of (acid and nonacid) reflux and symptoms such as apnea, cough and respiratory symptoms. However, the test is expensive and is not readily available.

Endoscopy with histology can determine the presence and severity of esophagitis, strictures and Barrett's esophagus. It is also useful to rule out other conditions such as eosinophilic esophagitis and acid peptic disease including gastritis or peptic ulcers which may present with similar symptoms as GERD. Therefore, endoscopy has become the test of choice for children with reflux

symptoms in many centers in USA. At endoscopy, erosions or ulcers of distal esophagus indicate severe esophagitis. Histological criteria of reflux esophagitis include presence of eosinophils, basal zone hyperplasia and increased papillary length.

There are other tests to assess GER and complications, but are not used routinely. Gastric scintigraphy is a nuclear medicine scan used to assess gastric emptying and reflux of nonacidic gastric contents. A lack of standardized technique and absence of age specific normative data limit the value of this test. Bronchoscopy may show lipid-laden macrophages suggestive of pulmonary aspiration secondary to reflux.

In adults, an empiric trial of proton pump inhibitor (PPI) is routinely used. Although not well studied in children, empiric trial of PPI for up to 4 weeks is justified in older children with classical symptoms of GERD such as heartburn or regurgitation. However, a long-term PPI therapy without a specific diagnosis is not recommended.

MANAGEMENT

For physiologic reflux of infancy, reassurance to parents is the most important part of the management as reflux improves with time and without any intervention. Smaller and more frequent feeds are beneficial in infants with GER. Frequent burping during feeds as well as keeping infants in an upright position after feeding is recommended. Thickening of formula feeds with rice cereal can decrease the number of episodes of vomiting in infants. Acid suppression medications can be used, but are not recommended. Therapeutic strategies for the management of GER in older children are shown in **Table 3**.

General Measures

Elevation of the head of the bed is recommended for older children with nocturnal reflux symptoms. Children should be advised to avoid acidic fruit juices, caffeinated beverages, chocolate and fatty foods as these tend to make reflux symptoms worse. Exposure to smoking can also worsen reflux symptoms and therefore should be avoided. Weight loss is beneficial in obese children with reflux.

Acid Suppression Therapy

It is commonly used as first line therapy for significant reflux. Antacids directly buffer gastric acidic contents and reduce heartburn and reflux symptoms. They can be used on as needed

Table 3 Therapeutic strategies for gastroesophageal reflux (GER)

Lifestyle changes	<ul style="list-style-type: none"> Positioning Avoidance of smoking exposure Weight reduction in obese children Dietary changes
Antacids	<ul style="list-style-type: none"> Aluminum hydroxide/magnesium carbonate 10–20 mL as needed Aluminum hydroxide/magnesium hydroxide 10–20 mL as needed
H ₂ RA	<ul style="list-style-type: none"> Famotidine 1 mg/kg/day divided bid; Max 40 mg/day Ranitidine 6–8 mg/kg/day divided bid; Max 300 mg/day
PPI	<ul style="list-style-type: none"> Omeprazole 1–3 mg/kg/day, Max 40 mg daily Lansoprazole 1–3 mg/kg/day, Max 60 mg daily Pantoprazole 20–40 mg daily Esomeprazole 10–40 mg daily Rabeprazole 10–40 mg daily
Surgery	<ul style="list-style-type: none"> Nissen fundoplication Laparoscopic fundoplication

Abbreviations: H₂RAs, histamine 2 receptor antagonists; PPI, proton pump inhibitor.

basis, but regular long-term use is not recommended. Acid suppressants such as histamine 2 receptor antagonists (H₂RAs) and proton pump inhibitors (PPIs) act to decrease esophageal acid exposure by reducing the quantity of gastric acid secretion. H₂RAs block histamine receptors on the parietal cell while PPIs block the Na-K-ATPase enzyme (proton pump), which is the final common pathway of acid secretion. While both H₂RAs and PPIs are effective in the healing of esophagitis and symptomatic relief of reflux symptoms, PPIs are superior to H₂RAs. PPIs should be given 30 minutes before breakfast to get maximum efficacy. The duration of therapy should be 3–6 months and an attempt should be made to withdraw these medications after that time.

Flow chart 1 shows algorithm for treating children with GER symptoms who have no risk factors for chronic GERD. High-risk group of children often require long-term therapy for months to years for ongoing severe GERD. In children with GERD and asthma, chronic cough can predispose to reflux and reflux can cause reflex bronchospasm. Therefore, it is prudent to treat both conditions simultaneously for symptomatic relief. Adverse effects related to H₂RA and PPIs are generally mild and rare. They include headache, diarrhea and constipation. Tachyphylaxis can develop with H₂RAs and therefore they should not be used for long-term therapy. PPIs are generally well tolerated over long-term (up to 11 years). Some patients taking them for prolonged periods may develop mild to moderate hypergastrinemia. Even though gastric carcinoids have been shown in some animal studies, they have not been shown in humans. The secretion of intrinsic factor is also inhibited along with that of acid. However, megaloblastic anemia due to vitamin B₁₂ deficiency is rare, which reflects the large stores of the vitamin in the body.

Prokinetic Agents

Metoclopramide (dopamine-2 and 5-HT₃ antagonist), domperidone (D₂ receptor antagonist), cisapride, mosapride and renzapride (selective 5HT₄ agonists) and erythromycin (motilin receptor agonist) are commonly used in adults with GERD to improve esophageal motility and gastric emptying. However, they

cannot decrease TRLES which plays a key role in the pathogenesis of GER. Cisapride may cause QT prolongation, arrhythmia and Torsades de pointes, and has been withdrawn from many countries. Hence, prokinetic agents are not recommended currently in children due to their doubtful efficacy and risk of adverse effects.

Other Drugs

The selective GABA agonist *baclofen*, which is used in children with spasticity, inhibits TRLES, and is hence useful in GERD. It also reduces postprandial acid and nonacid reflux and its associated symptoms. However, it may cause fatigue, confusion and insomnia and there are only very few studies in children. Drugs like salbutamol, theophylline, diazepam and barbiturates, which can precipitate or aggravate reflux should be avoided in children with GER.

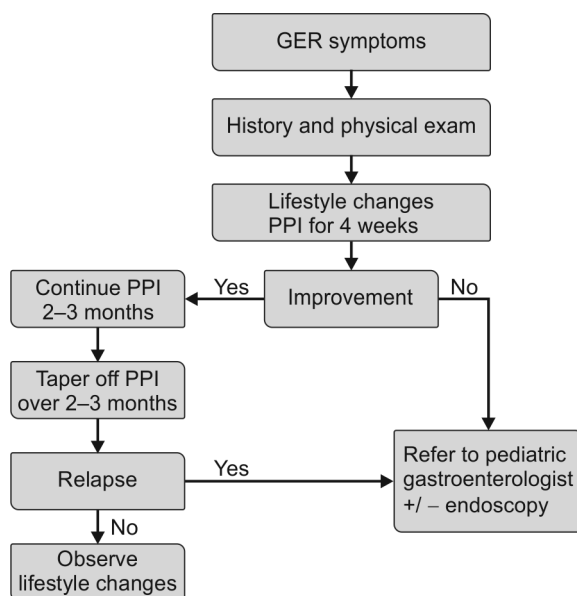
Surgical Therapy

It is indicated for intractable reflux despite medical management and life-threatening aspiration. The most common procedure is fundoplication in which a part of stomach is wrapped around the lower esophagus to prevent reflux. Nissen fundoplication is the most common operation performed. Fundoplication has a high success rate in the otherwise normal children with reflux. However, in a high-risk group of children with severe GERD, fundoplication is associated with a significant rate of failure and complications. In this group of children PPIs have been shown to be effective, even after failure of fundoplication. Recently laparoscopic fundoplication has been gaining popularity due to shorter postoperative stay. Overall, with the availability of proton pump inhibitors, necessity of fundoplication has decreased considerably.

PROGNOSIS

Physiologic reflux of infancy usually does not need any major therapeutic intervention and has excellent prognosis. Children with GERD respond well to dietary advice and PPI therapy. Children in high-risk group can develop severe GERD and complications and often require combination of long-term PPI therapy and surgery.

Flow chart 1 Approach to GER in older children



Abbreviations: GER, gastroesophageal reflux; PPI, proton pump inhibitor.

IN A NUTSHELL

1. Gastroesophageal reflux is common in infancy and disappears by 1 year of age in most cases.
2. Gastroesophageal reflux of infancy is diagnosed by history and does not require any tests or major therapeutic intervention.
3. Children with neurologic impairment, chronic respiratory disorders, obesity and history of repaired esophageal atresia are at high-risk for developing severe GERD.
4. Gastroesophageal reflux in older children presents as vomiting, regurgitation and heartburn.
5. Gastroesophageal reflux can lead to esophagitis and may be associated with asthma and other respiratory complications.
6. Esophageal pH study and impedance study can be helpful to assess correlation of GER and extraesophageal symptoms.
7. Endoscopy with histology is the best test to diagnose esophagitis.
8. Acid suppression with H₂RA and PPI are effective in healing esophagitis and providing symptomatic relief.
9. Children with high-risk for GERD require a long-term PPI therapy.
10. Surgery for GERD is reserved for severe aspiration or failure of medical therapy.

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Chapter 35.9

Umbilical Hernia

Prakash Agarwal

Umbilical hernia is herniation of the intestine through the umbilical ring (**Fig. 1**). Umbilical hernia is commonly seen in infants, which may herald an underlying problem or in most of the cases may be just a routine finding and settles down on its own.

EPIDEMIOLOGY

Umbilical hernia in children has an equal frequency in boys and girls. A slightly higher incidence is reported in Africa and African-American infants. The incidence is around 75% in low birthweight infants, which will spontaneously close over time. The incidence is higher in patients with Down syndrome, Trisomy 18, Trisomy 13, mucopolysaccharidosis, and congenital hypothyroidism. It may also be a part of Beckwith-Wiedemann syndrome.

ETIOLOGY

Defect in the underlying fascia below the umbilical ring leads to an umbilical hernia.

PATHOGENESIS

During development of the fetus the umbilical cord passes into the abdomen through the umbilical ring. After birth, the opening in the abdominal muscles closes as the baby matures. Sometimes, these muscles do not meet and grow together completely, and there is still a small opening present. A loop of intestine can move into the opening between abdominal muscles and cause a hernia.

An umbilical hernia in children is surrounded by a dense layer of fascia through which a peritoneal sac attached to the overlying skin protrudes; this is known as direct umbilical hernia. Usually the umbilical ring continues to close over time and the fascia of the umbilical defect strengthens, which accounts for the spontaneous resolution of this defect in most children. An indirect umbilical hernia is one in which the peritoneal contents herniate superior to the umbilical ring. The hernia follows the umbilical canal along the umbilical vein, the linea alba anteriorly, and a thin layer of preperitoneal fascia in a posterior direction. This form of hernia is

also known as proboscoid hernia (**Fig. 2**). Hernia of the umbilical cord is one in which there is a defect in the peritoneum and the fascia leading to intestine herniating into the substance of the umbilical cord (**Fig. 3**).

CLINICAL FEATURES

Umbilical hernias do not usually cause pain. They are present at birth but may become more noticeable when the child is bearing down—crying, coughing, or straining to have a bowel movement. The bulge may seem to disappear when the child is quiet or resting. Umbilical hernia with a small ring diameter (< 1.0 cm) is more likely to close spontaneously and earlier than those with a ring diameter of more than 1.5 cm. Incarceration of intestine or omentum, strangulation, perforation, evisceration and pain are rare events in the natural history in the umbilical hernia of children.

MANAGEMENT

Umbilical hernia is a clinical diagnosis and usually does not require any investigations to confirm the diagnosis. Routine blood investigations are required before proceeding for surgery in order to rule out anemia and bleeding profile. A thyroid profile may be



Figure 2 Proboscoid umbilical hernia



Figure 1 Typical presentation of an umbilical hernia



Figure 3 Hernia of the umbilical cord

done to rule out congenital hypothyroidism. An ultrasound may be done to rule out intra-abdominal tumors or ascites.

Indications for surgery We usually observe umbilical hernia and manage conservatively till 2 years of age. Rare event of incarceration requiring reduction, strangulation, perforation, evisceration are absolute indications for surgery. Infant with giant proboscoid hernia in whom the umbilical ring does not narrow may be considered for repair before 2 years. Typical umbilical hernia should be observed until the age of 2 years. Sometimes the most difficult task is to convince the family that observation alone will be successful in most cases and that the hernia may resolve spontaneously by 2 years of age. If the child has an obstructed umbilical hernia it is reduced by milking the air out of the incarcerated loop of intestine and applying firm pressure on the mass. One episode of obstruction should prompt the surgeon to operate immediately. If reduction is not possible then emergency surgery is required. If an infant is having both inguinal and umbilical hernia, the umbilical hernia should be left alone as it may close spontaneously.

Surgery for umbilical hernia Standard procedure for umbilical hernia repair involves multilayer closure of the peritoneum and fascial layer. A small curved incision (resembling a smile) will be made under your child's belly button. Absorbable and nonabsorbable sutures are used in the repairs. The redundant skin may be left in place to resolve over a period of time. Usually repair of umbilical hernia is performed as a day care surgery after infiltrating the wound with local anesthesia. Complications of umbilical hernia repair may be infection of the repaired wound, recurrence of the hernia and rarely visceral injuries.

After surgery, the child's umbilicus may appear to be slightly swollen, but this will resolve over the next few weeks. The child should be advised not to participate in physical education or sports for 2–3 weeks after surgery.

IN A NUTSHELL

1. Umbilical hernia is herniation of the intestine through the umbilical ring.
2. Umbilical hernia may be of three types, an indirect umbilical hernia, proboscoid hernia and hernia of the umbilical cord.
3. Incarceration of intestine or omentum, strangulation, perforation, evisceration and pain are rare.
4. Umbilical hernia with a small ring diameter (< 1.0 cm) is more likely to close spontaneously and sooner than those with a ring diameter of more than 1.5 cm.
5. Umbilical hernia is a clinical diagnosis and usually doesn't require any investigations for confirmation of the diagnosis.
6. Indications for surgery in umbilical hernia are, umbilical hernia not resolving spontaneously by 2 years, proboscoid hernia and incarcerated umbilical hernia.

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Chapter 35.10

Constipation

Praveen Kumar, Preeti Singh

Constipation is a feeling of unsatisfactory defecation—hard stools, passage of too small stools or too difficult to expel. North American Society of Pediatric Gastroenterology, Hepatology and Nutrition has defined chronic constipation as *delay or difficulty in defecation present for 2 or more weeks which causes significant distress to the patient*. If inadequately treated, it may lead to chronic abdominal pain, loss of appetite, and fecal incontinence. In addition, it can also make the child under confident and socially secluded. Constipation is generally under-reported because of lack of lucid definition and embarrassment to seek medical advice. The reported prevalence varies from 0.3% to 30%, depending upon the definition used in the study.

NORMAL PHYSIOLOGY

There is a wide variation in stool according to age and diet. Some breastfed infants may defecate after each feed, while others may have infrequent soft bowel movements (2–14 days). In infants and young children defecation is a simple spinal reflex and social training brings control of the reflex by higher centers. Most children achieve voluntary control of stool by the age of 2–3 years. Bowel continence is primarily maintained by internal and external anal sphincters. The involuntary internal anal sphincter which is the thickened circular smooth muscle at the levator ani flexure, receives innervations from parasympathetic splanchnic nerves (inhibitory) and sympathetic (excitatory) nerves. Internal sphincter relaxes when the rectum gets distended. The external anal sphincter which is under voluntary control consists of somatic skeletal muscle innervated by the pudendal nerve. It is maintained in a state of tonic contraction unless the person has the desire and the place is conducive. Another important anatomical landmark is puborectalis muscle which makes a sling around the lower part of rectum. Puborectalis gets inserted into symphysis pubis and is responsible for maintaining the normal anorectal angle of 85–100 degree. During defecation, this angle becomes straight or obtuse in squatting position to ensure smooth passage of stool. Rectal distension with feces initiates reflex contractions of its musculature with initiation of the desire to defecate. Subsequently voluntary defecation is initiated by relaxation of the external anal sphincter with expulsion of the rectal contents. Difficulties with defecation result from dysfunction in any part of the normal anatomy or physiology of defecation.

PATHOPHYSIOLOGY

The desire to defecate is activated when stool comes into contact with lower rectal mucosa. In the absence of favorable environment to defecate, there is failure of relaxation of the external anal sphincter and feces keep getting accumulated higher in the rectal vault further abolishing the defecation reflex. With progressive stool accumulation over a period of time, the rectum dilates leading to loss of sensation and effective propulsive movements required for evacuation. The retained stools become harder and difficult to pass causing painful defecation and development of anal fissure. This further reinforces stool withholding behavior, thus leading to a vicious cycle. The retentive posture is an attempt to avoid defecation in which the infant typically screams with facial flushing, exhibit stiffening of the body with arching of back and contraction of gluteal muscles. Similarly toddlers and older

children stand straight and stiff, or hold onto furniture, cross their legs, walk on tiptoes to withhold stools till the defecation urge passes off. These signs are often misinterpreted by parents as straining to pass stools. If this persists for a long duration, watery stools may leak around the large fecal mass causing involuntary soiling or encopresis.

DEFINITIONS

Functional constipation The Rome III criteria for diagnosis of functional constipation depends on the age of the child and is given in **Box 1** and **2**.

Encopresis Encopresis is the involuntary passage of formed, semi-formed or liquid stool in the child's underwear after achieving age of continence. This may be a complication of chronic constipation.

Intractable constipation Constipation not responding to optimal conventional management given for 3 months.

ETIOLOGY

Organic causes accounts for only 5–10% cases, but there are a large number of conditions which can cause constipation (**Box 3**). Constipation is labeled as functional or idiopathic when it cannot be explained by organic causes. Functional constipation is responsible for 90–95% of chronic constipation in children. The most common organic cause in young children is Hirschsprung disease (HD) accounting for 6% of all patients.

Functional constipation during childhood is a result of a complex interplay of developmental transitions, environmental factors and parental response. Retention of stools starts in response to a number of relatively innocent events like voluntary retention to avoid school toilets, protest against bowel training, diet lacking fiber or temporary illness, anal fissure, etc. If an acute episode of constipation is not managed appropriately, it leads to chronic constipation.

BOX 1 The Rome III criteria for functional constipation in neonates and toddlers*

- < 2 defecations per week
- > 1 episode per week of incontinence after the acquisition of toileting skills
- History of excessive stool retention
- History of painful or hard bowel movements
- Presence of a large fecal mass in the rectum
- History of large-diameter stools that may obstruct the toilet
- For a child with a developmental age < 4 years, at least 2 of the above symptoms must occur for at least 1 month.

* Hyman PE, Milla PJ, Benninga MA, et al. Gastroenterology. 2006;130:1519–26.

BOX 2 The Rome III criteria for functional constipation in children and adolescents*

- Two or fewer defecations in the toilet per week
- At least one episode of fecal incontinence per week
- History of retentive posturing or excessive volitional stool retention
- History of painful or hard bowel movements
- Presence of a large fecal mass in the rectum
- History of large diameter stools that may obstruct the toilet.
- For a child with a developmental age > 4 years with insufficient criteria for irritable bowel syndrome, ≥ 2 criteria fulfilled at least once/week for at least 2 months before diagnosis.

* Rasquin A, Di Lorenzo C, Forbes D, et al. Gastroenterology. 2006;130:1527–37.

BOX 3 Etiology of constipation

- **Functional constipation** (85–95%)
- **Organic causes** (5–15%)
 - *Abnormalities of colon and rectum*
 - Chronic intestinal pseudo-obstruction
 - Pelvic or sacral mass
 - Anal stenosis
 - Anal or colonic stricture—post NEC or IBD
 - Postsurgical repair of imperforate anus
 - Anteriorly placed anus
 - *Neuropathic lesions of the gastrointestinal tract*
 - Hirschsprung disease
 - Intestinal neuronal dysplasia
 - *Spinal cord lesions*
 - Spina bifida
 - Meningomyelocele
 - Sacral agenesis
 - Diastematomyelia
 - Spinal cord tumors (lipomas, cysts)
 - *Metabolic causes*
 - Diabetes mellitus
 - Diabetes insipidus
 - Hypothyroidism
 - Hypercalcemia/hypocalcemia
 - *Neurologic causes*
 - Cerebral palsy, autism
 - *Drugs*
 - Analgesics, antacids, anticholinergics, lead toxicity
 - Bismuth, iron, cholestyramine, psychotropics
 - *Others*
 - Celiac disease, cystic fibrosis, cow milk protein allergy.

Abbreviations: NEC, neonatal necrotizing enterocolitis; IBD, inflammatory bowel disease.

CLINICAL PRESENTATION

Although many children are brought with difficulty in defecation or infrequent bowel movements, others present with a variety of symptoms like recurrent abdominal pain, vomiting, abdominal distension, abdominal mass, blood-streaked stools or excessive flatulence. Infants and toddlers may present with irritability. Mothers may sometimes give history of straining while passing stools, posturing (squeezing of buttocks, scissoring or crossing of their legs) with some children even having loose stools from encopresis.

EVALUATION

A thorough history and physical examination (**Table 1**) is essential for differentiating functional constipation from an organic cause. Examination of the perineum and perianal area is important. Abdominal examination may reveal a lump in the left iliac fossa or suprapubic area due to retention of fecal matter in the sigmoid and descending colon. Development and psychological history (interaction with siblings and peers, temperament, any disruption of family life) helps in identifying underlying cause. Family history of chronic gastrointestinal diseases like inflammatory bowel disease, irritable bowel syndrome should also be enquired.

The *Red Flags Signs*, helpful in identifying an organic disease are given in **Table 2**. One of the most important organic causes of constipation during neonatal period is HD. Important clinical pointers in an affected infant include abdominal distension, pencil—thin hard pellet like stool and failure to thrive. While delayed passage of meconium beyond 48 hours is very suggestive, 50% of babies with HD do pass meconium within 48 hours of birth. Delay in treatment can lead to development of enterocolitis. Delayed passage of stools is also seen in hypothyroidism and cystic fibrosis. While delayed passage of meconium, symptoms since first month of life and abdominal distension are more common in children with organic cause, fecal impaction is more in functional group.

Digital rectal examination (DRE) reveals hard fecal matter in acquired constipation while it is empty in HD. A typical finding seen in HD is gush of fecal matter on withdrawal of fingers. DRE requires expertise, privacy and informed consent. Present guidelines do not support the routine use of DRE to diagnose functional constipation.

Flow chart 1 presents an algorithm for evaluation of constipation.

INVESTIGATIONS

Most children with functional constipation with or without fecal incontinence do not require any laboratory work-up apart from a careful history and physical examination.

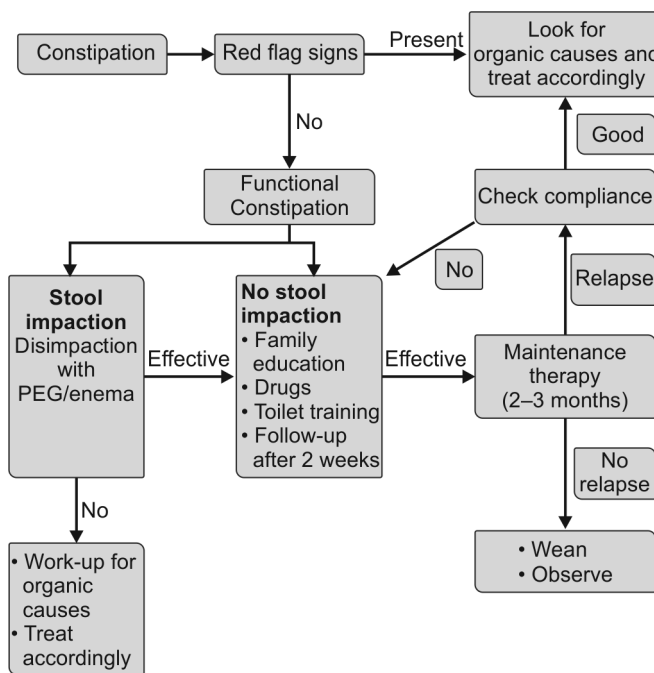
Rectal biopsy Rectal suction biopsy is the gold standard for the diagnosis of HD. It is performed around 3 cm above the anal verge, deep enough to include the submucosa. The aganglionic segment is recognized by absence of ganglion cells in submucosa and the presence of hyperplastic nerve trunks. There is absence of both ganglion cells and hypertrophied nerves in total colonic aganglionosis. Hyperganglionosis and/or ectopic ganglion cells are features of neuronal intestinal dysplasia.

Table 1 Evaluation of constipation

History	Physical examination
Stooling habits <ul style="list-style-type: none"> • Frequency, amount, diameter, and consistency of stools • Age of onset of constipation • Character of stools in toilet and underwear • Stool withholding maneuvers • Fecal incontinence 	Anthropometry: Weight, height Abdominal examination: Distension, palpable fecal mass
Any precipitating factors Change of diet, timing of/toilet training or some events such as infections, fissure, starting nursery/school, major change in family conditions	Neurological examination Tone, strength of lower limbs, deep tendon reflexes, cremasteric reflex, perianal sensation testing
Abdominal pain, vomiting and distension, poor appetite and irritability Urinary complaints Day wetting Bed wetting History of urinary tract infections	Anal size and location Position, stool present around anus or on clothes Perianal erythema Skin tags Anal fissures
Dietary habits Diet low in fiber, poor intake of fluids, high intake of dairy products Drug history: Antispasmodics, codeine containing cough preparations	Digital rectal examination Anal wink, anal tone, presence or absence of stool, consistency of stool, explosive stool on withdrawal of finger

Table 2 Red flag signs indicating organic causes of constipation

Clinical features	Diseases
Delayed passage of meconium (after 48 hours after birth), small-caliber stools, failure to thrive, tight anal sphincter, empty rectum with palpable abdominal fecal mass, gush of air and liquid stool may follow withdrawal of the examining finger	Hirschsprung disease
Abdominal distention, bilious vomiting, ileus	Pseudo-obstruction
Decreased lower extremity tone and/or strength	Spinal cord abnormalities
Absence or delay in relaxation phase of lower extremity deep tendon reflexes, absence of anal wink and cremasteric reflex or presence of pilonidal dimple or hair tuft	
Abnormal position or appearance of anus	Imperforate anus, anal stenosis, anteriorly displaced anus
History of delayed passage of meconium, fatigue, cold intolerance, bradycardia, poor growth	Hypothyroidism
Polyuria, polydipsia	Diabetes insipidus
History of delayed passage of stool, failure to thrive, fever, recurrent pneumonia	Cystic fibrosis
Chronic/recurrent diarrhea, pallor, abdominal distension	Celiac disease
Diarrhea, failure to thrive, occult blood positivity	Cow's milk protein intolerance

Flow chart 1 Algorithm for evaluation of constipation

Imaging Plain X-ray abdomen will help diagnose fecal impaction, the presence of which has implications in management. An unprepared barium enema will demonstrate a transition zone (more prominent in older children due to prolonged stool retention) separating dilated, stool-filled normally innervated ganglionic segment from an empty abnormal or aganglionic bowel segment. It is not a valid alternative to gold standard rectal biopsy.

Anorectal manometry When the above investigations are inconclusive, anorectal manometry helps in diagnosing abnormalities of defecation. Normal individuals will demonstrate relaxation of internal anal sphincter in response to rectal distension (rectoanal inhibitory reflex). This reflex gets abolished in HD and in patients with internal sphincter achalasia. In latter group, a rectal biopsy is normal despite a nonrelaxing internal anal sphincter. Other functional problems like pelvic floor dyssynergia and neurosensory rectal abnormalities can also be diagnosed using anorectal manometry.

Colonic transit study Dysfunctional (pan or segmental) colonic motility can be evaluated using radiopaque markers during colonic transit study. It is a precise tool for evaluation of colonic motor function and helps differentiate myopathy from neuropathic causes. Neuropathy is characterized by nonpropagating, disordered high amplitude contractions or an absence of the gastrocolic response while absent or weak colonic contractions is suggestive of myopathy.

MANAGEMENT

Acute constipation Identify any precipitating cause. Treat local causes like anal fissure, boil, dermatitis, etc., if any. Encourage use of high fiber diet-cereals, pulses, vegetables and fruits. Prescribe laxatives for short duration (7–10 days). Encourage toilet training if not already done.

Chronic constipation Patients with an identifiable organic cause for constipation should be appropriately treated medically or surgically. Treatment of functional constipation requires multimodality approach and includes education of parents and counseling; disimpaction and bowel cleansing; maintenance therapy; and follow-up. These measures have already been discussed in the chapter on encopresis (see section 21).

The drugs used in management of constipation are listed in **Table 3**. The first line of management of a child who presents with constipation and fecal impaction is disimpaction using polyethylene glycol (PEG) orally at a dose of 1–1.5 g/kg/day for 3–6 days. PEG is not degraded by bacteria; is not readily absorbed and thus acts as an excellent osmotic agent. If PEG is not available then disimpaction may be achieved with once a day enema for 3–6 days. Phosphate enema is better than normal saline enema. Other alternatives are glycerin suppositories in infants and bisacodyl suppositories in older children. Hospitalization may be required to treat children with severe disimpaction particularly when oral PEG is not tolerated. Such children are given nasogastric lavage and are closely monitored for abdominal distension and dyselectrolytemia during the disimpaction. Maintenance therapy (PEG 0.4 g/kg/day) is then started to maintain normal stool frequency of once or twice a day. It is important to ensure good therapeutic compliance otherwise recurrence of stool impaction can restart the constipation cycle. Maintenance therapy should be continued for at least 2 months and it should then be gradually weaned and discontinued after ensuring resolution of symptoms for at least 1 month. Parents are advised to ensure adequate water intake and daily servings of a variety of fiber-rich foods such as whole grain

Table 3 Drugs used for the treatment of constipation in children

Oral laxatives	Dose	Side effects
A. Osmotic laxatives		
Lactulose	1–2 mL/kg body weight twice/day	Bloating and abdominal distension
PEG 3350 with electrolytes	1–1.5 g/kg/day for 3–6 days (disimpaction)	Nausea, bloating, cramps and vomiting
PEG 3350 without electrolytes	Maintenance: 0.2–0.8 g/kg/day	
Milk of magnesia (magnesium hydroxide)	2 mL/kg body weight twice/day for 7 days (disimpaction) 2–5 years: 0.4–1.2 g/day, once or divided 6–11 years: 1.2–2.4 g/day, once or divided 12–18 years: 2.4–4.8 g/day, once or divided	Abdominal distension, hypermagnesemia, metallic taste. Avoid in renal failure
B. Fecal softeners		
Mineral oil	3 mL/kg body weight twice/day for 7 days (disimpaction) 1–18 years: 1–3 mL/kg/day, once or divided, max 90 mL/day	Not for infants Lipoid pneumonia if aspirated
C. Stimulant laxatives		
Bisacodyl (Oral)	3–10 years: 5 mg/day > 10 years: 5–10 mg/day	Abdominal pain, diarrhea
Bisacodyl (Suppository)	2–10 years: 5 mg once/day > 10 years: 5–10 mg once/day	Abdominal pain, skin rash, fixed drug eruption rarely
Senna	2–6 years: 2.5–5 mg once or twice/day 6–12 years: 7.5–10 mg/day	Abdominal cramps, diarrhea
Sodium picosulfate Tab 10 mg, syrups 5 mg/5 mL	1 mo–4 years: 2.5–10 mg once/day 4–18 years: 2.5–20 mg once/day	
Rectal laxatives/enemas		
Sodium docusate (lubricant)	< 6 years: 60 mL, > 6 years 120 mL	Cramps, abdominal pain
Sodium phosphate enema	1–18 years: 2.5 mL/kg, max 133 mL/dose	Hyperphosphatemia, hypernatremia, hypokalemia, hypocalcemia and dehydration
NaCl	Neonate < 1 kg: 5 mL, > 1 kg: 10 mL > 1 years: 6 mL/kg once or twice/day	
Glycerin suppository	Infants and toddlers	No side effects

breads and cereals, fruits, vegetables, and legumes in diet to ensure adequate fiber (required: age in years + 5 g/day).

Follow-up Children and their parents are instructed to maintain a record of daily bowel movements, and medication use. After regular bowel habits are established the drug dosage is gradually decreased to ensure one soft bowel movement per day. Follow-up is recommended at 1 month, 3 months, 6 months and then 3–6 monthly intervals to ensure optimal response.

Patients with *refractory or recurrent constipation* in spite of good compliance to the prescribed therapy will require detailed work-up. Metabolic tests such as serum calcium, thyroxine or thyroid-stimulating hormone, and celiac disease should be carried out. MRI of the lumbosacral spine can exclude occult spinal cord abnormalities and colonic manometry will detect occult myopathy or neuropathy. Full-thickness rectal biopsies will reliably exclude HD or neuronal intestinal dysplasia.

PROGNOSIS

Conventional treatment with adequate fiber and laxatives, toilet training is successful in approximately in 60% of cases. Adequate dose and treatment adherence is more important than which laxative is used. Good prognostic indicators are better compliance, adequate intake of roughage diet and self-confidence. Poor prognostic indicators include severe motor disability, mental retardation, school time soiling and neurogenic causes.

IN A NUTSHELL

1. Constipation is a common problem in children which can present with infrequent and or painful defecation, fecal incontinence and abdominal pain.
2. Functional constipation is most common cause accounting for 90–95% of cases.
3. Most children with functional constipation with or without fecal incontinence do not require any laboratory work-up apart from a careful history and physical examination. Presence of red flags increases possibility of underlying organic cause.
4. The most common organic cause in young children is Hirschsprung disease accounting for 6% of all patients.
5. Treatment of functional constipation requires multimodality approach and includes education of parents and counseling; disimpaction and bowel cleansing; maintenance therapy; and follow-up.
6. The first line of management of a child who presents with constipation and fecal impaction is disimpaction using polyethylene glycol (PEG) orally at a dose of 1–1.5 g/kg/day for 3–6 days.
7. Maintenance therapy should be continued for at least 2 months and it should then be gradually weaned and discontinued after ensuring resolution of symptoms for at least 1 month.

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Chapter 35.11

Hirschsprung Disease

Ketan Parikh

Hirschsprung disease (HD) is characterized by a congenital aganglionosis of a variable length of the distal colon extending proximally from the anorectal junction. The incidence ranges from 1:4,000 to 1:7,000 newborns in various series. The disease is usually sporadic but occasionally runs in families. Male:female ratio is 4:1 however in females the length of the aganglionic bowel is often longer. HD usually presents with chronic constipation.

PATHOGENESIS

Normal peristaltic activity involves a wave of relaxation preceding a wave of contraction. Parasympathetic innervation is essential for this wave of relaxation. In HD, the parasympathetic ganglia are absent from the Meissner's and Auerbach's plexuses of the affected bowel. The aganglionic bowel is normal in caliber but because of the absence of the peristaltic activity, the wave of relaxation is absent thus leading to a functional obstruction. The chronic obstruction leads to massive dilatation and hypertrophy of the normally ganglionated proximal bowel. The junctional portion of the bowel often shows a section of hypoganglionosis with partial function. The mucosa in the proximal hypertrophied portion of the bowel may show ulceration and hyperplasia due to chronic inflammation due to stagnation.

CLASSIFICATION

Depending on the length of the segment of aganglionosis, the disease is categorized as *short segment* (aganglionosis restricted to either the rectum or the rectosigmoid); *long segment* (extending more proximally to colon); *total colon* (entire colon); *very long segment* (a portion of the small bowel is also aganglionic); *total bowel* the entire bowel (small and large) is aganglionic—almost incompatible with normal life) and *ultrashort segment* (aganglionosis restricted only to the terminal portion of the rectum).

CLINICAL FEATURES

At birth, there is failure to pass meconium for more than 48 hours after birth and gradual onset of intestinal obstruction. Even if the baby passes meconium with some assistance, he again may get obstructed. There may be a persistent passage of meconium even until 1 week of life.

In case the disease does not manifest at birth, it presents later with constipation dating back to early infancy. Intestinal obstruction may manifest at any age which may be relieved by enemas. Rarely, attacks of foul smelling diarrhea interspersed with constipation may confuse the picture. In chronic cases—child fails to thrive and is malnourished. Abdominal distension is marked and the transverse colon is often visible. On rectal examination—the rectum is felt to be empty, and on withdrawal of the examining finger, there is an explosive passage of flatus and feces.

DIAGNOSIS

Most of the diagnostic techniques for HD have been described in the previous chapter on constipation. A plain X-ray of the abdomen may show features of intestinal obstruction—large dilated colon loops. It may also show absence of rectal gas shadow. Barium enema reveals a narrow aganglionic segment

and a cone-shaped colon at the junction of the ganglionic and aganglionic segments (**Figs 1 and 2**). Anorectal manometry may strongly suggest the diagnosis of HD. The final confirmation is only with a full thickness biopsy of the rectal wall which will show absence of ganglion cells.

TREATMENT

Conservative treatment involving repeated enemas/suppositories may help in overcoming an acute attack of intestinal obstruction and may help to postpone the surgery. However, many infants may not respond at all to conservative treatment and may need an emergency surgery. In such a case, an emergency colostomy may be the only option to save the child.

The principle of the surgery is the removal of the aganglionic segment of colon and ensuring that normal ganglionic bowel is anastomosed to the terminal rectum as close as possible to the anal canal. Traditionally this surgery is done in stages but in recent years, single stage surgery is being done with variable success rates.

Various commonly performed surgeries include the modified Duhamel's procedure, Swenson's procedure and Soave's procedure. Either of these may be performed by regular laparotomy or by laparoscopic methods.



Figure 1 Barium enema showing narrow segment in classical Hirschsprung disease
Source: Dr Praveen Kumar, New Delhi.



Figure 2 Barium enema of Hirschsprung disease showing the cone

IN A NUTSHELL

1. Hirschsprung disease (HD) should be suspected in any apparently normal newborn who fails to pass meconium in the first 24 hours.
2. Hirschsprung disease should be suspected in any child who has repeated attacks of enterocolitis (profuse explosive diarrhea) interspersed with constipation.
3. Most patients with HD do not have soiling/encopresis.
4. A palpable fecaloma—low in the rectum is not likely to be due to HD.
5. Rectal biopsy is diagnostic of HD.

MORE ON THIS TOPIC

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Chapter 35.12

Chronic Abdominal Pain

B Bhaskar Raju, Sumathi Bavanandam

Abdominal pain is a common complaint in pediatric practice, with at least 15% of all outpatients suffering from it. *Recurrent abdominal pain* (RAP) which troubles the child periodically with pain-free intervals in between, is so common, that the term RAP was used as a specific diagnosis for several decades, to refer to a condition wherein, pain occurs at frequent intervals with no organic cause made out on examination or investigation. Today, the same is referred to as *chronic abdominal pain* (CAP). Functional abdominal pain, which is the most common form of CAP seen in clinical pediatric practice, has been discussed here. There are many organic and nonorganic causes of abdominal pain in children within and outside the gastrointestinal tract (GIT); they will be touched upon, but not discussed in detail, since that would be beyond the scope of this chapter.

CHRONIC FUNCTIONAL ABDOMINAL PAIN

Even though functional abdominal pain is a benign disorder, it is something to be taken seriously since it troubles the child and the whole family. It has to be clearly differentiated from malingering, wherein the child feigns pain for some reward like avoiding school or homework, or just for the sake of sympathy. Functional abdominal pain is true pain that is actually felt by the child. Chronic functional abdominal pain (CFAP) may also present as functional dyspepsia; irritable bowel syndrome; abdominal migraine; or a combination of the above.

Chronic functional abdominal pain is a specific diagnosis to be made after ruling out all anatomic, infectious, inflammatory and metabolic causes of abdominal pain. Presence of red flag signs and symptoms should warn the physician to make every effort to rule out organic causes of CFAP. The final diagnosis of CFAP will always depend upon a good clinical history, and a thorough physical examination of the child, besides evaluation of precipitating and reinforcing factors in the family and immediate environment of the child.

DEFINITIONS

Any abdominal pain that exceeds 8 weeks in duration is said to be chronic. Previous definitions of RAP insisted on presence of pain-free intervals and number of bouts of pain are obsolete. Apley and Naish, who were the first to scientifically study children with abdominal pain syndrome as early as 1958, defined RAP as three or more episodes of abdominal pain that occurred over 3 months, that were severe enough to interfere with the child's daily activities. Rome III criteria, which clarifies and defines all functional disorders of GI system in adults, children and infants, has two pediatric categories based on age. It defines CAP as any pain recurrent or continuous, lasting beyond 8 weeks.

PREVALENCE

Functional gastrointestinal disorders (FGID) account for more than 50% of consults in pediatric gastroenterology practice and a significant proportion is CFAP. CFAP is diagnosed in 2–4% of all cases in general pediatric practice in the West. Epidemiological studies in Europe and America have shown prevalence rates of RAP/CAP varying between 0.5% and 19% among school going children. Apley and Naish found that the incidence of detectable pathology in RAP was less than 8%. Among growing children

10–15% experience RAP over 8 weeks, sometime in their life, with the highest prevalence in middle school girls. However, many Indian and Pakistani studies which screened children for CAP in schools that cater to poorer socioeconomic strata, found a disproportionately high incidence (84%) of minor organic pathology in their cohort of CAP children, giardiasis being the most common. Given the ubiquitous nature of giardiasis in poorer societies, this finding is understandable. Studies from India and Sri Lanka that looked at CAP in urban settings with more hygienic environments reflect Western numbers; 74–76% of CAP being nonorganic. In Malaysia, the prevalence of CAP in urban and rural population-based cohorts is 9.6% and 11%, respectively, most of it being functional. Abdominal migraine affects 1–4% of school going children in the West, with girls being affected more than boys; mean age of onset is 7 years, peaking at 10–12 years.

PATHOPHYSIOLOGY

Functional CAP is essentially a disorder of gut-brain neural cross talk. Gut has more neurons and complicated neural interconnections than even the brain in higher primates. The *enteric nervous system* (ENS) as it is called, consists of two major collections of neurons called (1) Auerbach's plexus which is essentially a myenteric system controlling GI motility and (2) the Meissner's plexus which is essentially a submucosal system that controls secretions and has sensory functions as well. The interstitial cells of Cajal which are interspersed between the nerve endings and smooth muscles of GIT, act as pace makers, regulating propagation of intestinal contractions. ENS is responsible for the motor, sensory and vascular responses of the entire GIT to intrinsic and extrinsic stimuli and it extensively interacts with the central nervous system (CNS) through the vagus nerve. The ENS and CNS profoundly influence each other and abnormalities in ENS and its response to the CNS inputs are the basis for the pain felt in CFAP.

Recent research on the pathophysiology of functional bowel disorders focuses on two disordered physiological functions in children with CFAP—(a) heightened response to visceral pain (visceral hyperalgesia); and (b) disturbed bowel motility.

Visceral hyperalgesia This is otherwise known as augmented visceral perception or visceral hypersensitivity. This refers to the capacity of children with CFAP to feel events in the gut that are otherwise usually imperceptible to normal children. Signals from Meissner's plexus are generally filtered at the hypothalamus (hypothalamic gate) and very few signals make their way for perception by the cortex. This explains why most intestinal activity is not felt. Children with CFAP however, feel physiological events like peristalsis, postprandial and gaseous distension of gut, as pain, thanks to augmented visceral perception. Many studies have documented enhanced awareness and pain in response to balloon distension of the rectum in these children. Almost a third of them also have autonomic disturbances with pain episodes, like dizziness, headaches, vomiting, pallor, temperature intolerance, also indicating the role of the nervous system in CFAP. Mucosal inflammatory processes secondary to infections, allergy, and primary inflammatory diseases may also cause sensitization of afferent nerves and visceral hyperalgesia, resulting in augmented visceral pain perception. This explains the often elicited history that the CAP started with a bout of diarrhea and vomiting.

Altered intestinal motility Besides augmented visceral perception, children with CFAP have significantly increased amplitude of both peristaltic and nonperistaltic contractions of intestine. Levine's famous hypothesis tries to understand this phenomenon of increased cortical stimulation of gut musculature through his conceptual model of CFAP (**Fig. 1**). This model suggests various external and intrinsic stimuli can trigger inappropriate contractions

of the bowel, felt as pain by the child. The normal function of the CNS is to integrate all interoceptive inputs from gut and elsewhere in the body, and accordingly send back efferent neuronal signals to GIT which trigger myoactivity in the intestines. Aberrations in this integration and response from the CNS result in inappropriate and enhanced bowel contractions felt as pain by the child.

Levine's Hypothesis

Levine suggests CFAP is triggered and induced by several intrinsic and extrinsic inputs inducing pain in a susceptible child who has heightened sensitivity to visceral sensations and increased bowel activity secondary to CNS inputs (**Fig. 2**).

Lifestyle and habits Regular eating habits, an active lifestyle including exercise and regular bowel habits improve CFAP symptoms, lack of them predispose to CFAP.

Temperament and learned responses Learned responses refer to children who respond poorly to discomfort and pain with exaggerated responses because of being petted and pampered. They do not take disappointment well. If secondary gain is involved, their expression of discomfort worsens. For example, allowing children to skip school on account of pain makes pain episodes worse and more frequent.

Somatic predisposition Chronic functional abdominal pain tends to run in families (Pain families). This may have a genetic predisposition, but it is more likely that there is modeling involved. Children mimic their parents' complaints and tendency to complain and grumble.

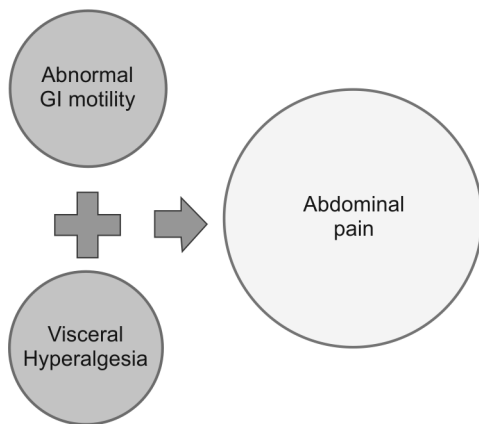


Figure 1 Schematic representation of pathophysiology of functional abdominal pain (FAP)

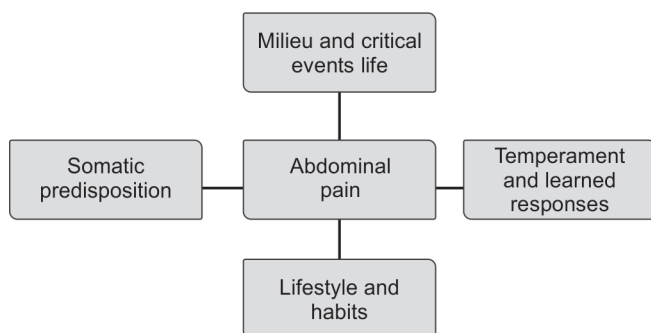


Figure 2 Environmental factors and cortical stimulation of increased gut activity

Milieu and critical events These refer to several events in a child's life, besides examinations, that can be stress triggers for pain. Loss of a friend, relocation to a new home and family discord can all precipitate pain episodes.

CLINICAL PRESENTATION

In the 80s, all RAPs were classified as organic (10%) or psychogenic (90%). Later psychogenic pain was split into dysfunctional abdominal pain (95%), and RAP due to psychiatric problems (5%). Dysfunctional abdominal pain is presently called CFAP. Given the complexity of presentation of FGID, attempts were made to streamline, define and clarify these disorders. The third committee on functional disorders of GIT (adults, children and infants) met in Rome and published the scholarly treatise on FGID, called Rome III criteria for FGIDs in 2006. As per Rome III criteria, all childhood functional abdominal pain disorders are one of four types:

1. **Functional dyspepsia:** This is characterized by rapid gastric emptying associated with slow bowel transit. Children with this disorder have poor appetite, dyspepsia and postprandial bloating as predominant symptoms, instead of pain.
2. **Irritable bowel syndrome (IBS):** Symptoms of IBS include altered stool frequency (four or more stools/day or two or less stools/week), abnormal stool form (lumpy/hard or loose/watery stool), abnormal stool passage (straining, urgency, or feeling of incomplete evacuation), passage of mucus and bloating or feeling of abdominal distension. Abdominal pain may or may not be a part of the syndrome.
3. **Abdominal migraine:** Defined as severe paroxysmal periumbilical pain, often intense, lasting 1 hour or more, interspersed with pain-free intervals, lasting weeks to months. Investigations fail to reveal any evidence of inflammatory, anatomic, metabolic, or neoplastic process attributable for subject's symptoms. Pain interferes with normal activities and pain episodes are associated with two or more of the following symptoms like anorexia, nausea, vomiting, headache, photophobia, or pallor.
4. **Childhood functional abdominal pain:** Characterized by episodic or continuous abdominal pain (mild to moderate) with insufficient criteria for other FGIDs, in the absence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the subject's symptoms.

(Criteria to be fulfilled at least once per week for at least 2 months before diagnosis).

FUNCTIONAL ABDOMINAL PAIN SYNDROME (FAPS)

The term syndrome is used for functional abdominal pain, if at least 25% of pain episodes include, interference with daily activities, sleep disturbances, other somatic symptoms like headache and limb pains (criteria to be fulfilled at least once per week for at least 2 months before diagnosis).

Typical pain pattern in functional pain is characterized by paroxysmal nature of pain with variable severity; clustering of pain; gradual onset; usually periumbilical, occasionally epigastric location; poor relationship to food, defecation and inability to clearly describe nature or localize the pain. It may be associated with other symptoms like pallor/nausea/fatigue/anxiety in about 10% of the cases. It should be differentiated from the typical pain pattern in organic pain which is well defined and clearly localized, away from the umbilicus, and may be radiating. Burning, stabbing pain; pain awakening the child at night; pain with fever; pain with weight loss; tenderness/organomegaly; blood in stools (occult or obvious); altered bowel movements; anemia, urinary symptoms, increased erythrocyte sedimentation rate/C-reactive protein

(ESR/CRP) and associated arthralgia/rash/purpura are the red flag signs that should immediately warn the physician that he could be dealing with an organic pathology, requiring diligent investigations to identify it.

EVALUATION

History, clinical examination and the presence or absence of red flag signs/alarm symptoms, help to differentiate between organic and nonorganic causes of pain in clinical practice. Many studies especially in India, have picked up conditions like constipation, gastroesophageal reflux disease (GERD) esophagitis, *Helicobacter pylori* (*H. pylori*) gastritis, lactase deficiency, and rarely inflammatory bowel disease (IBD) and celiac disease, in what was clinically diagnosed to be functional abdominal pain. As a general rule, if the pattern of abdominal pain appears functional, with a completely normal history and physical examination without occult blood or parasites in stool and bowel movements are normal, a physician is justified in diagnosing CFAP without extensive investigations. But, he must follow-up the child closely, however, and whenever red flag signs appear or pain relief is not observed with time, he must order investigations to rule out organic causes.

Besides a detailed history and physical examination, all cases of suspected CFAP require evaluation of the child's interpersonal relationship with the rest of family especially parents, siblings, grand parents and friends; child's immediate emotional environment in school and home; child's personality; child's response to discomfort and pain; sociability and school performance/problems.

INVESTIGATIONS

Majority of cases of CFAP can be picked up on clinical examination and most do not require investigations other than stool microscopy and occult blood. Where pain in CFAP has been long-standing, and reassurance does not result in relief of pain, investigations are order of preference are listed in **Box 1**.

Before a child is finally labeled CFAP, it is wise to keep in mind some conditions that cause RAP, but may be easily missed by both clinical examination as well as by investigations. These include GERD (may be missed if not biopsied), *H. pylori* gastritis (requires biopsy), constipation, chronic appendicitis/appendicular colic, giardiasis/pinworms, leukemia (iliac bone pains), hernias (linea alba) and spinal lesions.

MANAGEMENT

Principles of management are summarized in **Box 2**. The goal of therapy does not include complete relief of pain which may not be possible in short-term. Reassurance of the parents and child that nothing is wrong with him/her is the cornerstone of therapy in CFAP. Most children with CFAP tolerate pain better, once reassured there is nothing seriously wrong and the parental anxiety about pain disappears. The aim should be to have normal school attendance and scholastic and sports activities to the child's potential. Counseling by the pediatrician usually achieves all these. Some severe cases that do not respond to reassurance and counseling may need additional modalities like:

- Cognitive behavioral therapy
- Psycho education
- Relaxation based therapy.

Dietary management includes reduction in sugary foods, sodas and irregular eating habits. Increase in fiber intake also helps. Food allergies are increasing in incidence and a good dietary history might unravel food allergies. If found, avoidance will help. Lactose intolerance, which is an important cause of RAP in Caucasian population, is, however, rare in India beyond infancy.

BOX 1 Investigations for chronic pain abdomen

Level I investigations

- Complete hemogram
- Serum amylase/lipase/liver and renal function tests
- Stool and urine analysis
- Screening for tuberculosis
- Ultrasonography (USG) of abdomen

In the absence of red flag signs, when the above set of investigations are normal, one can label the child as having CFAP. If the above investigations fail to pick up any pathology and the child presents with one or more red flag signs, additional investigations may be needed (*Level II investigations*). Pain with altered bowel movements, occult blood positive in stool, anemia, ↑ESR/CRP, fever, rash and recurrent aphthous ulcers, merit direct visualization of the bowel, both upper and lower.

Level II investigations

- Contrast studies of upper and lower GIT
 - Upper and lower GI endoscopies, including appropriate biopsies
- Inability to identify a cause with level II investigations, with persistence of pain occurred in less than 1% of cases in our series. They will need third level investigations to identify rarer causes of recurrent abdominal pain.

Level III investigations

- EEG to rule out abdominal epilepsy and cyclical vomiting disorder
- Screening for porphyrias/lead poisoning/collagen vascular disorders/lactose intolerance/food allergies/motility disorders.

Abbreviations: CFAP, chronic functional abdominal pain; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; EEG, electroencephalogram.

BOX 2 Principles of management of chronic abdominal pain

- Arriving at a positive diagnosis
- A detailed explanation of the pathophysiology and the cause of pain to parents and child
- Establishing goals of therapy and explaining that complete relief of pain is not one of them
- Identification and modification of triggers and physical or psychological stress
- Diet modification
- Drug therapy in selected cases
- Active psychological support
- Avoidance of hospitalization
- Avoidance of psychiatric consults, unless strong evidence for an underlying psychiatric disorder exists.

Medications

Drugs are uniformly useless in CFAP except in selected situations. Functional dyspepsia may respond to proton pump inhibitors (PPIs) and prokinetics and so does documented acid peptic disease including GERD. Antispasmodics are best avoided in CFAP, except in IBS with a significant pain component. They precipitate gastroesophageal reflux and constipation. Peppermint oil has been found useful in IBS and some cases of CFAP. Stool softeners benefit children with constipation. Abdominal migraine if suspected, would do well with pizotifen. Recently, many trials have looked at probiotics like *Lactobacillus* GG, *Bifidobacterium*, VSL#3, and have reported mixed results. Antimotility agents are best avoided, except in severe diarrheal forms of IBS. In endemic areas, empirical metronidazole therapy for giardiasis might help. Routine deworming has no role in CFAP therapy. Treatment of *H. pylori*, even when identified in biopsy has had only equivocal effect. Typical CFAP does not need antipsychotic medication. Psychiatric consult often scares the parents and child and worsens the pain and may be avoided, unless an underlying psychiatric disease is suspected. A multidisciplinary team including a psychiatrist will

be needed in the following situations: conversion reaction; low self-esteem; anxiety, depression; maladaptive family; modeling/imitating family behavior; or poor response to conservative therapy.

PROGNOSIS

About 70% of CFAP children have complete relief of pain without any medication, with just a positive diagnosis and reassurance that there is nothing seriously wrong with them. Many do get recurrences, but they too remit well. About a third of them grow into adulthood with abdominal pains. An equal number develop new symptoms like headaches, back pains, etc. CFAP children, however, handle pains much better as they grow into adulthood.

CHRONIC ABDOMINAL PAIN: ORGANIC CAUSES

It is beyond the scope of this chapter to deal with all pathology that could present with CAP, but some guidelines are given as to what diseases to screen for depending on presentation of the pain.

Child presenting with isolated periumbilical paroxysmal pain (IPUPP) Screen for renal/biliary/pancreatic colic, malrotation, abdominal epilepsy, intussusception, vasculitis (Henoch-Schönlein purpura), porphyrias, less than 5% of children with IPUPP actually have an organic basis. Others are functional in origin.

Child presenting with CAP and significant dyspepsia GERD, peptic ulcer disease, *H. pylori* infection, giardiasis, pancreatitis and motility disorders.

Child presenting with CAP and altered bowel movements Simple constipation, IBDs, abdominal tuberculosis, immunodeficiency syndromes, intestinal lymphomas, eosinophilic enteritis, postoperative adhesions and congenital band obstructions.

Almost one-third of patients with CAP and significant altered bowel habits will have an organic basis for the pain, the rest will be functional.

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IN A NUTSHELL

1. The term RAP is now replaced by CAP.
2. Chronic functional abdominal pain is a specific diagnosis, made after ruling out anatomic, infectious, inflammatory, or metabolic causes of abdominal pain.
3. Chronic functional abdominal pain includes functional dyspepsia, irritable bowel syndrome, abdominal migraine, and FAPS.
4. A clinical diagnosis of CFAP can be made in children between 4 years to 18 years of age when alarm symptoms/signs are absent and physical examination is normal, provided stool microscopy and occult blood test are negative.
5. Alarm symptoms requiring investigations include involuntary weight loss, linear growth deceleration, anemia due to GIT blood loss, significant vomiting, chronic diarrhea, persistent right upper or lower quadrant pain, unexplained fever and any family history of inflammatory bowel disease.
6. Alarm signs that require investigations include localized right upper or lower quadrant tenderness, localized fullness, mass, organomegaly, costovertebral angle tenderness, spine tenderness, and perianal abnormalities like fistula or abscess.
7. Investigations are indicated if pain significantly decreases quality of life and interferes with routine activities, even if alarm signs and symptoms are absent.
8. Psychological factors should be addressed during diagnostic evaluation and management and if found contributing to pain, should ideally be handled by counseling by pediatrician.
9. Time-limited use of medications, such as acid-reduction therapy, antispasmodic agents, smooth muscle relaxants, low doses of psychotropic agents, nonstimulant laxatives or antidiarrheals may be appropriate in selected cases to decrease symptom frequency or severity.
10. The role of antidepressants (tricyclics, selective serotonin reuptake inhibitors) in the treatment of FGIDs associated with abdominal pain needs to be assessed.

Chapter 35.13

Acid Peptic Disease

R Bhanu Vikraman Pillai

Acid peptic disease is one of the important treatable causes of abdominal pain. The term encompasses esophagitis, gastritis, peptic ulcer disease and duodenitis. It is important to identify these causes and treat them appropriately for the resolution of symptoms as well as prevention of certain conditions with lifelong implications. Acid peptic diseases are relatively common causes of abdominal pain in children, but are less common than chronic constipation or irritable bowel syndrome. Peptic ulcer disease, either primary or secondary, is an important but uncommon cause of abdominal pain in children compared to adults. Since gastroesophageal reflux disease (GERD) as well as *Helicobacter pylori* (*H. pylori*) infection is described in detail elsewhere, we will restrict our discussion to the rest of the spectrum.

PATHOPHYSIOLOGY

It is important to recall the different types of cells in the stomach and their functions. In the body and fundus of the stomach, they include the chief cells producing pepsinogen, parietal cells producing acid and intrinsic factor, enterochromaffin-like cells producing histamine, enterochromaffin cells secreting serotonin and D-cells secreting somatostatin. The antrum contains mucus glands, gastrin secreting G-cells, some D-cells and enterochromaffin cells.

The pathophysiology of peptic disease involves the imbalance between the aggressive and protective factors of the gastric mucosa. Gastric acid and pepsin are the major aggressive factors. Acid secretion is an active process in the parietal cells by the enzyme H^+/K^+ -ATPase, which is the proton pump. In term neonates, acidification of the gastric contents occurs soon after birth. The acid production gradually increases and reaches adult levels by 24 weeks. Gastric acid production is increased in duodenal ulcers but not in gastric ulcers. The bicarbonate-mucus barrier protects the mucosa from the acid-pepsin attack. The gastric epithelial cells secrete mucus continuously, and most importantly it is stimulated by the prostaglandins. The mucus barrier forms the *unstirred layer* and lies directly over the epithelial cell layer and protects the mucosa from the harmful effects of acid and pepsin. The mucin glycoprotein at the luminal side of the unstirred layer is broken down by pepsin, but is replaced by the continuous production of mucus by the epithelial cells. However, when there is a disruption of mucus production by infections, ischemia or noxious agents such as nonsteroidal anti-inflammatory drugs (NSAIDs), it predisposes the mucosa to attack by the acid and pepsin that could result in peptic ulcer disease.

ETIOLOGY

There are several causes for gastritis in children. By strict definition, gastritis is a histologic diagnosis and should have inflammatory cells; but in gastropathy, there is mucosal injury without significant inflammation. However, the terms gastritis and gastropathy are used together since the clinical symptoms are similar. The causes of gastritis or gastropathy in children are listed in **Box 1**; few important ones are discussed here.

Infection *H. pylori* is well known to cause of gastritis. It can cause nodular gastritis, erosions, as well as peptic ulcer disease. World Health Organization (WHO) has classified *H. pylori* as a group 1 carcinogen as it is associated with adenocarcinoma as well as lymphoma arising from mucosa-associated lymphoid tissue

BOX 1 Causes of gastritis in children

- Stress gastritis
- *Helicobacter pylori* gastritis
- Nonsteroidal anti-inflammatory drugs-induced gastritis
- Other drug-induced gastritis including iron
- Crohn's disease
- Eosinophilic gastritis
- Allergic gastritis
- Cytomegalovirus gastritis
- Corrosive-induced gastritis
- Graft versus host disease
- Gastritis associated with chronic granulomatous disease
- Bile gastropathy
- Gastritis associated with autoimmune disorders
- Pernicious anemia
- Radiation-induced gastritis
- Collagenous gastritis
- Gastric lymphoma (mucosa-associated lymphoid tissue lymphoma).

(MALToma) of the stomach. These are fortunately very rare in children. In addition to *H. pylori*, *H. heilmannii* infection has also been implicated in gastritis. *H. pylori* infection is discussed in detail elsewhere.

Drugs Nonsteroidal anti-inflammatory drugs are very frequently prescribed medications in rheumatologic conditions and can result in a spectrum of mucosal damage ranging from microscopic changes to frank ulceration and bleeding or even perforation. Cyclooxygenase (COX)-catalyzes conversion of arachidonic acid to prostaglandins. The beneficial and harmful effects of NSAIDs are due to their ability to inhibit this reaction. The most common site of NSAID-induced damage is the stomach, but it certainly can damage the small bowel, colon as well as esophagus. The prostaglandins produced by COX-1 pathway are responsible for hemostasis and mucosal integrity; while those produced in the COX-2 pathway are responsible for pain, fever and inflammation. The nonselective NSAIDs such as aspirin, ibuprofen, indomethacin, diclofenac, mefenamic acid and meloxicam inhibit both pathways, and are more likely to cause GI side effects. The COX-2 inhibitors such as celecoxib or rofecoxib are less likely to cause GI side effects, but are not totally safe. As NSAIDs are protein-bound, hypoalbuminemia increases the serum levels of free drugs which increase the risk for toxicity.

Allergy Food allergies can cause eosinophilic gastritis as well as eosinophilic esophagitis. It can be isolated or be part of eosinophilic gastroenteritis. In children, the proteins of cow's milk, soy, wheat and egg are the most commonly encountered allergens. Peripheral eosinophilia may or may not be seen. Ménétrier's disease is a rare disorder with giant, hypertrophied gastric folds with excessive mucus production and protein-losing gastropathy. This could be associated with cytomegalovirus (CMV) infection. In children, it is considered benign and self-resolving, whereas in adults it can be an acquired premalignant condition.

Graft versus host disease (GVHD) Acute GVHD which occurs between 21 days and 100 days after transplantation may present with nausea, vomiting, diarrhea and abdominal pain and GI bleed. GVHD usually occurs after allogeneic bone marrow transplantation, but rarely after solid organ transplant also. They have characteristic histologic features. Chronic GVHD rarely involves the stomach. Pernicious anemia is associated with body-predominant atrophic gastritis, and results in loss of secretory function of acid, pepsinogen as well as intrinsic factor causing achlorhydria and anemia from vitamin B₁₂ deficiency. These patients have antibodies against parietal cell components.

Crohn's disease may cause gastritis resulting in abdominal pain, hematemesis, melena and delayed gastric emptying. Up to 30% patients with Crohn's disease have histologic evidence of gastritis with granulomas. Granulomatous gastritis can also occur in chronic granulomatous disease of childhood.

Zollinger Ellison (ZE) syndrome is caused by gastrinomas and has fasting hypergastrinemia, usually greater than 125 pg/mL, resulting in hyperchlorhydria. ZE syndrome can be sporadic, or associated with multiple endocrine neoplasia type 1 (MEN1). Gastrinomas can occur in pancreas as well as stomach, duodenum, liver and kidney. In addition to refractory peptic ulcerations, ulcerations may occur in unusual locations such as jejunum. They present with abdominal pain, diarrhea, heartburn, weight loss as well as GI bleeding. ZE syndrome associated with MEN1 presents with nephrolithiasis in addition to abdominal pain, heartburn and GI bleeding. Pseudo-ZE syndrome or G-cell hyperplasia also causes hypergastrinemia, hyperchlorhydria as well as peptic ulcerations, but there is no response to gastrin stimulation, unlike in ZE syndrome.

CLINICAL PRESENTATION

Epigastric pain is an important symptom of acid peptic disease in children. It may be associated with vomiting and nocturnal awakening. The temporal relationship with food is noted only in 50% of children with peptic ulcer disease. Some children may present with upper gastrointestinal (GI) bleed in the form of hematemesis or melena, while some may have associated heartburn, weight loss or iron deficiency anemia. Occult GI bleeding in a child with abdominal pain and vomiting needs to be investigated for possible peptic ulcer disease or other etiologies such as inflammatory bowel disease or eosinophilic disorders.

PRIMARY VERSUS SECONDARY PEPTIC ULCER DISEASE

Peptic ulcer disease can be classified as primary or secondary, based on whether or not there is an underlying systemic disease. Most primary peptic ulcers develop between 8 years and 17 years of age, whereas the secondary peptic ulcers can develop at any age. Even though *H. pylori* associated peptic ulcer is rare in children, it is the most common cause of primary peptic ulcer disease. Less commonly, ulcer can develop even if *H. pylori* is negative. Up to 29% of duodenal ulcers can be *H. pylori* negative. Hence, when *H. pylori* is ruled out by more than one test and there is no history of recent NSAIDs or antibiotics, ZE syndrome and G-cell hyperplasia, which can also cause primary peptic ulcer disease, should be excluded.

DIAGNOSIS

The definitive diagnosis of gastritis and peptic ulcer disease is by upper GI endoscopy (**Fig. 1**) and biopsy. The diagnosis of *H. pylori* is discussed elsewhere. Barium studies are not relevant currently given the high rates of false-negatives as well as false-positives. However, barium contrast studies are useful in identifying complications such as gastric outlet obstruction. If there is suspicion of ZE syndrome due to persistent peptic ulcers, further investigations like computed tomography, magnetic resonance imaging as well as radionuclide octreotide scanning and selective arterial secretin testing to locate the gastrinoma may be necessary.



Figure 1 Duodenal ulcer

TREATMENT

The treatment of *H. pylori* is discussed elsewhere. Acid suppression is the mainstay in the treatment of gastritis as well as peptic ulcer disease. In addition to acid suppression, treatment specific to the etiology such as avoiding NSAIDs when possible is essential. Ulcerations from Crohn's disease require immune modulator therapy. Eosinophilic gastritis would need avoidance of the allergic foods and at times corticosteroid therapy. Proton pump inhibitors (PPI) are very effective in acid suppression and are now the preferred drugs for acid suppression. There are sufficient data on the safety and efficacy of PPIs in children, even though most of the studies are done in patients with GERD. H_2 -receptor antagonists such as ranitidine and famotidine may be used, but are less effective than PPIs and many patients develop tolerance or tachyphylaxis. Sucralfate may be used for short term, and in acid pH, the molecule dissociates and binds to damaged tissue. It contains aluminum and should be used with caution in renal failure.

Diet should be modified so as to avoid carbonated and caffeinated drinks that increase acid secretion. Every effort should be made to discourage and stop cigarette smoking which predisposes to ulcer formation and complications, probably by inhibition of prostaglandin synthesis.

Bleeding from the ulcer can usually be controlled endoscopically. However, at times one may need help from the interventional radiologist for hemostasis by coiling or embolization. Surgical treatment may be necessary for complications such as perforation, refractory bleeding and gastric outlet obstruction.

MORE ON THIS TOPIC

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IN A NUTSHELL

1. Acid peptic diseases are relatively common causes of abdominal pain in children, but less common than chronic constipation or irritable bowel syndrome. Peptic ulcer disease, either primary or secondary is important but uncommon cause of abdominal pain in children compared to adults.
2. The pathophysiology of peptic disease involves the imbalance of the gastric mucosal aggressive and protective factors.
3. The definitive diagnosis of gastritis as well as peptic ulcer disease is by upper GI endoscopy and biopsies.
4. Both the primary and secondary causes of gastritis require treatment of the underlying pathology as well as acid suppressive therapy.
5. Acid suppressive therapy is best achieved by PPI and is effective and safe in children.

Chapter 35.14

Pancreatitis

A Riyaz, Geeta M Govindaraj

ACUTE PANCREATITIS

Pancreatitis is inflammation of the parenchyma of the pancreas caused by the destructive effects of pancreatic enzymes, resulting in acinar cell injury. Traditionally considered a very rare disease in children, their numbers have increased over the past decade all over the world. This is possibly due to greater awareness of the disease among pediatricians. Ninety percent of children have acute pancreatitis and 10% chronic pancreatitis. However, pancreatitis being a mild disease in children unlike adults, the diagnosis may be easily missed, if the pediatrician is not aware of the problem.

CLASSIFICATION

Acute pancreatitis is a reversible process which does not cause any lasting effects on the pancreatic parenchyma or function. In contrast, *chronic pancreatitis* is a prolonged and frequently lifelong disorder secondary to fibrosis within the pancreas.

The *Atlanta classification* categorizes acute pancreatitis into mild and severe types. Mild acute pancreatitis has minimal organ dysfunction and has a self-limited course with an uneventful recovery. Severe acute pancreatitis consists of organ failure and/or local complications such as pseudocysts, necrotizing pancreatitis or abscess.

ETIOLOGY

The major causes of acute pancreatitis in children are infections, trauma, drugs and systemic diseases. This is in contrast to adults in whom it is caused mainly by gallstones and alcohol abuse, and to some extent by hypercalcemia and hypertriglyceridemia.

Infections

Viral infections that cause pancreatitis include mumps, rubella, varicella, measles, influenza, infectious mononucleosis, etc. Serum amylase and lipase may be elevated in about 70% children with mumps, but pancreatitis rarely occurs. Viral hepatitis, especially hepatitis A and B may also cause pancreatitis. Human immunodeficiency virus (HIV) infection causes pancreatitis by several mechanisms. The virus may directly affect the gland. Opportunistic infections caused by cytomegalovirus, *Mycobacterium avium-intracellulare*, *Mycobacterium tuberculosis*, *Cryptococcus neoformans* (*Torula histolytica*), *Cryptosporidium parvum*, *Toxoplasma gondii*, *Histoplasma capsulatum*, and *Candida* species may also cause pancreatitis. Pancreatic neoplasms like Kaposi's sarcoma and lymphoma seen in about 5% of patients with acquired immunodeficiency syndrome (AIDS) may also be responsible. Hydroxyurea as well as several antiretroviral drugs like stavudine and didanosine are notorious to cause pancreatitis. Hence, it is important to rule out HIV/AIDS in children with obscure pancreatitis.

Some bacteria like *Shigella*, *Campylobacter*, *Enterohemorrhagic Escherichia coli* 0157, *Legionella*, *Leptospira*, *Mycobacterium* and *Brucella* cause acute pancreatitis by releasing various toxins. There are several reports of severe pancreatitis complicating enteric fever. In developing countries like India, helminth infections caused by *Ascaris lumbricoides* (roundworms) may cause severe pancreatitis by blocking the main pancreatic duct and obstructing drainage of pancreatic secretions. It is difficult to diagnose and treat this condition. *Aspergillus fumigatus* and *Candida albicans* may also cause pancreatitis.

Systemic disorders The most important systemic disorder causing acute pancreatitis is hemolytic uremic syndrome, followed by sepsis, Kawasaki disease and Henoch-Schönlein vasculitis. Shock from any etiology may lead to pancreatitis by decreasing blood flow with resultant hypoxia. Reye's syndrome may be complicated by severe hemorrhagic pancreatitis. Children with collagen-vascular diseases including systemic lupus erythematosus (SLE), juvenile rheumatoid arthritis and polyarteritis nodosa, and inflammatory bowel disease like Crohn's disease and ulcerative colitis may also develop pancreatitis. However, many of these children may also be taking drugs known to cause pancreatitis, as part of the treatment of their primary disease.

Trauma The pancreas is not commonly damaged in blunt abdominal trauma as it is protected to some extent by its intraperitoneal location. Pancreatic damage is usually associated with injury to other organs, especially the liver and spleen. Bicycle handle-bar injury is an important cause of pancreatitis in children. It is important to rule out abuse in such cases. Traumatic pancreatitis should not be missed, as it may cause pancreatic duct transection, which may require surgical intervention.

Drugs are an uncommon but important cause of acute pancreatitis (**Box 1**). Drug-induced pancreatitis can be diagnosed only after excluding other causes of pancreatitis. There is usually an interval of 4–8 weeks between the initiation of treatment and onset of pancreatitis. Some drugs cause pancreatitis by a clear mechanism like inducing hypertriglyceridemia, which in turn causes pancreatitis. Pancreatitis can be reproduced on re-challenge with the same drug. One of the most commonly implicated drugs in children is *valproic acid*. The incidence of valproic acid-induced pancreatitis, however, is quite low.

Gallstones which are the most common cause of pancreatitis in adults, may sometimes cause pancreatitis in children, particularly those with congenital hemolytic anemia like thalassemia, sickle cell anemia, hereditary spherocytosis, etc. This should not be overlooked since endoscopic retrograde cholangiopancreatography (ERCP) may be indicated in such children.

Metabolic causes The important metabolic causes of pancreatitis include cystic fibrosis and familial hyperlipidemia types I, IV and V. Both acute and chronic pancreatitis may be seen in these cases. In hyperlipidemia, serum amylase and lipase levels will be normal and serum triglyceride levels will be more than 1,000 mg%. In cystic fibrosis, pancreatic duct may be obstructed due to viscous secretions, resulting in pancreatitis. Pancreas divisum is a relatively common congenital anomaly of the pancreatic ducts. It is caused by the failure of the ducts of the dorsal and ventral anlagen to fuse during the 5th and 6th week of gestation. Here, a major part of the exocrine pancreatic secretion drains through the accessory

BOX 1 Drugs causing pancreatitis in children

- Valproic acid
- Prednisone
- Isoniazid
- Carbamazepine
- Erythromycin
- Sulfonamides: mesalamine, 5-aminosalicylates, sulfasalazine, trimethoprim/sulfamethoxazole
- Metronidazole
- Stavudine
- Pentamidine
- Didanosine
- 6-mercaptopurine
- L-asparaginase
- Azathioprine
- Methyl dopa.

pancreatic duct of Santorini and the accessory papilla into the duodenum. It is usually asymptomatic, but about 10% of these children may develop acute pancreatitis.

Idiopathic Almost 25% of children with pancreatitis do not have any underlying etiology. They are labeled as having *idiopathic acute pancreatitis*, which is a diagnosis of exclusion. These children may develop recurrent attacks of pancreatitis.

PATHOGENESIS

The following four basic changes occur in pancreatitis, regardless of whether it is acute or chronic disease:

- Proteolytic destruction of pancreatic tissue
- Necrosis of blood vessels resulting in hemorrhage
- Necrosis of fat by lipolytic enzymes
- Associated inflammatory reaction.

Mild disease is characterized by peripancreatic fat necrosis and interstitial edema and the more severe form by intrapancreatic fat necrosis, parenchymal necrosis and hemorrhage. It may derange both endocrine and exocrine functions of the gland. The pancreatic acinar cells synthesize and store digestive enzymes until they are stimulated to secrete them into the ducts. All pancreatic enzymes, except amylase and lipase, are synthesized as proenzymes. The duodenum secretes an enzyme called *enterokinase* which activates trypsinogen to trypsin. Trypsinogen also has the capacity to slowly autoactivate to trypsin. Trypsin plays a major role in the pathogenesis of pancreatitis. It activates most proenzymes that participate in the process of autodigestion. Trypsin also activates prekallikrein to kallikrein which directly activates the kinin system and indirectly causes abnormalities in clotting and the complement system.

CLINICAL FEATURES

Most children with acute pancreatitis present with upper abdominal pain and vomiting. The pain is sudden in onset, with gradual increase in severity and reaches maximal intensity in a few hours. It may radiate to the back. The most common site is the epigastrium, followed by right hypochondrium, periumbilical area, back and lower chest. Pain is aggravated by food intake. Some children may have fever, tachycardia, hypotension, jaundice and abdominal signs like guarding, rebound tenderness and decreased bowel sounds. Many children with severe systemic illnesses causing pancreatitis refuse feeds. Hence acute pancreatitis should be ruled out, if a sick hospitalized child has worsening of clinical status with feed intolerance. Jaundice or elevated transaminases should raise the possibility of biliary tract involvement. Rarely, patients present with ascites or an abdominal mass. Epigastric tenderness is a useful, but nonspecific and unreliable sign. There are two rare clinical signs of hemorrhagic pancreatitis due to extravasation of hemorrhagic pancreatic exudate: Grey-Turner's sign—ecchymoses in the flanks; Cullen's sign—ecchymoses in the periumbilical region. These signs are more commonly seen in adults than children, and indicate a poor prognosis. Clinical features are summarized in **Table 1**.

It is difficult to differentiate sterile from infected acute necrotizing pancreatitis as both may result in fever, leukocytosis and severe abdominal pain. However, the differentiation is vital as the mortality rate in infected acute necrotizing pancreatitis is nearly 100% without intervention. The organism can be identified and appropriate antibiotic started with the help of CT-guided fine-needle aspiration and culture of pancreatic and peripancreatic tissue fluid.

The most important factor that determines management of pancreatitis following trauma is whether or not the pancreatic duct has been disrupted. The child with blunt trauma usually presents with mild epigastric pain, which may become severe as the pancreatic fluid leaks into the surrounding tissues. A high index of suspicion is essential as the clinical presentation can be

Table 1 Clinical features of acute pancreatitis

	Common	Rare
<i>Symptoms</i>	<ul style="list-style-type: none"> • Abdominal pain • Irritability in infants • Anorexia • Nausea • Vomiting 	<ul style="list-style-type: none"> • Jaundice • Fever • Feed intolerance • Respiratory distress
<i>Signs</i>	<ul style="list-style-type: none"> • Dehydration • Abdominal distension • Abdominal tenderness 	<ul style="list-style-type: none"> • Ascites • Pleural effusion • Grey-Turner's sign • Cullen's sign

quite deceptive. Serum amylase and lipase will be elevated in most children. A CT scan, or MRI cholangiogram may be a valuable diagnostic tool at this stage. Most of these children respond to conservative management alone. Surgery is indicated if there is disruption of the main pancreatic duct.

Complications

Acute pancreatitis is a self-limited disease and most children make an uneventful recovery. Mortality, if any, is due to complications of systemic illness. Major complications are summarized in **Table 2**. Pancreatic necrosis is a segmental pancreatic infarction which may result in serious complications. Fortunately, it is very rare, seen in less than 5% of adults and less than 1% of children. The risk of pancreatic necrosis increases with vascular leakage. The combination of hypovolemia, inflammation, and high hematocrit decreases pancreatic blood flow resulting in infarction. A contrast-enhanced CT reveals an area of under-perfused pancreatic gland. Pancreatic pseudocysts are rare in children compared to adults. They usually resolve spontaneously and drainage is usually not necessary.

APPROACH TO DIAGNOSIS

It is unfortunate that there is no gold standard for the diagnosis of pancreatitis. The diagnosis is based on a constellation of points in the history, clinical examination, supportive laboratory tests and imaging. Pancreatitis can be diagnosed based on the presence of two of the following:

- Abdominal pain suggestive of pancreatitis
- Serum amylase or lipase levels at least three times the upper limit of normal
- Radiologic evidence of acute pancreatitis.

Most children with acute pancreatitis will fulfill these criteria. However, infants and young children may not complain of abdominal pain. *Serum lipase* level is a very sensitive and specific marker of pancreatitis and considered as the first investigation of choice. Serum lipase will rise within 4–8 hour of onset, peak at 24 hour, and may remain elevated for 8–14 days before normalizing. In renal failure, renal excretion of lipase is decreased and hence it may increase up to twofold above normal. Lipase may leak from the intestine in perforation of the bowel and so it may increase up to threefold above normal.

Serum amylase level was the traditional, standard diagnostic test for pancreatitis. Levels will rise within 2–12 hours of onset, peak within the first 48 hours, and remain elevated for 3–5 days before returning to baseline. Even though it is a very sensitive test, its specificity is relatively low. Studies have shown that about 40% of cases of acute pancreatitis in children could be missed if diagnosis is based on amylase alone. Other causes of high amylase levels include intestinal obstruction, appendicitis, bowel perforation, acute cholecystitis and mesenteric ischemia, all of which come in the differential diagnosis of acute pancreatitis. In pancreatitis due to hypertriglyceridemia, serum amylase may be normal due to

Table 2 Complications of acute pancreatitis

Systemic (in the 1st week)	Local (after the 1st week)
Cardiovascular <ul style="list-style-type: none"> Shock—due to third spacing of fluids, peripheral vasodilatation, and depressed left ventricular function Arrhythmias Pulmonary <ul style="list-style-type: none"> Respiratory failure—due to ARDS and pleural effusion Renal failure Due to renal hypoperfusion, leading to acute tubular necrosis	<ul style="list-style-type: none"> Sterile pancreatic necrosis Infected pancreatic necrosis Pancreatic abscess Pseudocyst Rupture of pancreatic duct Pancreatic ascites Pleural effusion Sinistral (left sided) portal hypertension due to splenic vein thrombosis; presents as upper GI bleed due to ruptured gastric varices
Hematological DIC	
Metabolic <ul style="list-style-type: none"> Hypocalcemia Hyperglycemia—caused by insulin deficiency due to islet cell necrosis and/or hyperglucagonemia Hyperlipidemia 	
Gastrointestinal <ul style="list-style-type: none"> Ileus 	
Neurological <ul style="list-style-type: none"> Purtscher's retinopathy—sudden blindness due to occlusion of the posterior retinal artery by aggregated granulocytes Encephalopathy 	
Miscellaneous <ul style="list-style-type: none"> Arthralgia Subcutaneous fat necrosis—tender red nodules caused by elevated circulating lipase 	

Abbreviations: ARDS, acute respiratory distress syndrome; DIC, disseminated intravascular coagulation; GI, gastrointestinal.

the dilutional effects of the lipemia. Serum amylase reaches adult levels only by adolescence whereas serum lipase reaches adult levels after 1 year of age. Hence, lipase is more useful than amylase to diagnose acute pancreatitis in young children (**Table 3**).

The half life of amylase is relatively short (2 hours) and hence cleared rapidly from the circulation. If a child presents late in the course of the disease, the amylase peak may be missed and is one scenario where acute pancreatitis with a normal amylase occurs. Unlike amylase, serum lipase will be normal in diabetic ketoacidosis and in macroamylasemia. Many patients with pancreatitis have a selective elevation of either amylase or lipase at presentation. Hence, ideally, both amylase and lipase should be measured in patients with suspected acute pancreatitis. However, levels of amylase and lipase do not correlate with the severity of acute pancreatitis or its prognosis. Although not routinely available, serum trypsin level is the most accurate laboratory indicator of pancreatitis.

Complete blood count reveals leukocytosis. Hematocrit may be initially increased due to hemoconcentration. A low hematocrit may indicate hemorrhage or hemolysis. Serum electrolytes, blood urea nitrogen and creatinine help to determine the level of hydration especially in patients with intractable vomiting. Hyperglycemia may be caused by damage to the pancreas resulting in decreased

insulin secretion and increased release of glycogen, catecholamines and glucocorticoids. High serum aspartate aminotransferase (AST) and lactate dehydrogenase (LDH) are suggestive of tissue necrosis. Obstruction of the common bile duct may cause elevation of bilirubin and alkaline phosphatase. Hypoxemia may be caused by ARDS and pleural effusion and pH may be decreased due to lactic acidosis, respiratory acidosis and renal insufficiency.

It is essential to differentiate acute biliary pancreatitis which may require urgent ERCP with biliary sphincterotomy and stone extraction from nonbiliary conditions. If there is a threefold or more increase of alanine transaminase (ALT), biliary pancreatitis should be ruled out. The combination of elevated amylase/lipase and ALT may be more predictive of pancreatitis than elevated amylase or lipase alone. Fortunately, such cases are rare in children.

Role of imaging Plain erect abdominal radiograph may show nonspecific findings in pancreatitis like a generalized or local ileus (sentinel loop), or a colon cut-off sign. Rarely, calcified gallstones or pancreatic calcification may be seen. A chest radiograph may show pleural effusion and, in severe cases, a diffuse alveolar interstitial shadowing suggestive of acute respiratory distress syndrome (ARDS). Abdominal ultrasonography (**Box 2**) and CT scan help to document pancreatitis, determine the severity and detect complications like pseudocysts. They also identify any underlying chronic pancreatitis.

CT scan with intravenous and oral contrast helps to detect pancreatic necrosis which appears as nonperfused areas of pancreatic parenchyma. The presence of air within the pancreatic parenchyma suggests infection in the necrosed tissue. This should be confirmed with percutaneous needle aspiration and culture. MRI is useful in a pregnant adolescent (because of the radiation teratogenicity of CT), those who are allergic to the contrast used for CT, and those with renal failure which may be aggravated by the iodinated contrast. It is superior to CT in the characterization of pancreatic fluid collections. Magnetic

Table 3 Comparison between serum amylase and lipase for diagnosis of pancreatitis

	Amylase	Lipase
Sensitivity	Very high	Very high
Specificity	High	Very high
Time for elevation	2–12 hours of onset	4–8 hours of onset
Duration of elevation	3–5 days	8–14 days
Diabetic ketoacidosis and macroamylasemia	Increased	Normal
Utility in young children	Poor	Good

BOX 2 Ultrasonography (USG) findings in acute pancreatitis

- Enlargement and altered echogenicity of the pancreas
- Dilated main pancreatic duct; common and intrahepatic bile ducts
- Gallstones
- Biliary sludge
- Pancreatic calcification
- Choledochal cysts
- Fluid collections—peripancreatic or cystic.

resonance cholangiopancreatography (MRCP) delineates the bile and pancreatic ducts better than CT and has a higher sensitivity in detecting choledocholithiasis and pancreas divisum.

MANAGEMENT**Medical Management**

Treatment is essentially supportive, with the aim of alleviation of symptoms and prevention of complications. If an etiologic factor is identified, treatment should be directed at it. If the initial assessment is suggestive of mild pancreatitis, a conservative approach is indicated with intravenous fluids and frequent, but noninvasive, observation. No drugs (including antibiotics) are necessary, apart from analgesics. CT scanning is unnecessary unless there is evidence of deterioration. Early management steps are summarized in **Box 3**.

The most important cause of death is shock. Hence, the child's vital signs, urine output and central venous pressure should be monitored and corrected. They should be carefully observed for any signs of early organ failure like hypotension and pulmonary or renal insufficiency. Blood gas measurements and oxygen supplementation are mandatory if child has tachypnea. Children with signs of early organ dysfunction may deteriorate rapidly, and need to be cared for in an intensive care setting. Proper analgesia and intravenous fluids are the mainstay of management. Traditionally, opiates are used because of their potency. As morphine may increase the pressure in the sphincter of Oddi, meperidine 1–2 mg/kg IM/IV is preferred.

Capillary leak syndrome is common in children with severe acute pancreatitis. Hence, they may lose fluids from the vascular compartment. The situation may be aggravated if the stomach is decompressed by nasogastric aspiration. Unfortunately, in some centers, children with pancreatitis are kept fasting even today. Volume expansion is vital, as it provides cardiovascular stability, and also helps to prevent development of pancreatic necrosis. Recent studies have clearly shown that early feeding of patients with pancreatitis is beneficial. Enteral nutrition should commence within 24 hours of admission after fluid resuscitation and pain control. Several studies show that adult patients with acute pancreatitis tolerate jejunal feedings with fewer complications than those given parenteral nutrition. Antibiotics are usually unnecessary unless the child has developed pancreatic necrosis. There is no role for surgery during the initial period of resuscitation and stabilization; it is indicated only if the patient deteriorates due to local complications.

BOX 3 Early management of severe acute pancreatitis

- Meperidine—1–2 mg/kg IM/IV
- Aggressive IV fluid therapy
- Oxygen
- Frequent monitoring of vital signs, CVP, fluid intake output, blood gases
- Frequent monitoring of blood glucose, calcium, ALT, creatinine
- CT scan—indicated in clinical deterioration/septicemia/organ failure
- Early nasogastric feeding.

Abbreviations: IM, intramuscular; IV, intravenous; CVP, central venous pressure; ALT, alanine transaminase.

Hyperglycemia may complicate severe pancreatitis. However, it usually normalizes as the inflammatory process subsides, and blood sugar levels fluctuate widely. Hypoalbuminemia may lead to hypocalcemia which is usually asymptomatic and does not require any specific therapy. However, reduction in levels of ionized calcium may cause tetany. *Gabexate mesilate* is a trypsin inhibitor used to prevent or treat acute pancreatitis in adults. Gabexate infusion may be useful in children also.

Surgical Management

Surgery is usually not required and is limited to debridement of infected necrosed pancreatic tissue. Necrosectomy, if necessary for severe pancreatitis, is usually deferred for at least 2 weeks. In the rare instance of mild gallstone pancreatitis, cholecystectomy should be performed as soon as the child has recovered, but before the child is sent home. Abscess can be managed with intravenous antibiotics and external drainage. Surgery or endoscopic stenting may be necessary for traumatic rupture of the pancreatic duct.

CHRONIC PANCREATITIS

Chronic pancreatitis is a painful, destructive, inflammatory disease characterized by progressive fibrosis that leads to irreversible destruction of pancreatic tissue, culminating in exocrine and endocrine insufficiency. Histologic changes include irregular fibrosis, acinar cell loss, islet cell loss and inflammatory cell infiltrates.

ETIOLOGY

In children, chronic pancreatitis is usually caused by genetic diseases such as cystic fibrosis, hereditary pancreatitis or may be idiopathic (**Table 4**). This is in contrast to adults, in whom it is usually due to chronic alcoholism or is idiopathic.

Chronic pancreatitis may be secondary to mutations of several genes. Hereditary pancreatitis is an autosomal dominant disease due to mutations in the trypsinogen gene *PRSS1* that cause premature conversion of trypsinogen to trypsin. These children become symptomatic at a very young age and there is a high-risk of developing pancreatic cancer. *SPINK1* mutations are a common cause of tropical pancreatitis (TP). Severe homozygote mutations of the *CFTR* gene cause cystic fibrosis.

CLINICAL PRESENTATION

The most common presenting symptom of chronic pancreatitis is abdominal pain. A characteristic feature is the almost instantaneous aggravation of pain by food. Although food may also aggravate the pain of peptic ulcer, there is usually a much longer interval between the meal and the pain.

Nausea, vomiting, anorexia and weight loss are common in chronic pancreatitis. Weight loss is secondary to decreased caloric intake due to the fear of exacerbating the abdominal pain. Malabsorption, which occurs if enzyme secretion is reduced to less than 10% of normal, and uncontrolled diabetes may also contribute to weight loss. Such severe weight loss never occurs in other painful abdominal conditions like peptic ulcer. The combination of chronic upper abdominal pain and severe loss of weight should always alert the clinician to the possibility of an underlying chronic pancreatic disease.

DIAGNOSIS

Chronic pancreatitis can be diagnosed by histologic or morphologic criteria alone or by a conglomeration of morphologic, functional and clinical findings. Functional abnormalities alone are not diagnostic of chronic pancreatitis because these tests do not differentiate chronic pancreatitis from pancreatic insufficiency

Table 4 Causes of chronic pancreatitis

Hereditary pancreatitis
<ul style="list-style-type: none"> • CFTR mutations • SPINK1 mutations • Shwachman-Diamond syndrome
Metabolic causes
<ul style="list-style-type: none"> • Types I, IV and V hyperlipidemia • Hypercalcemia • Chronic renal failure
Autoimmune
<ul style="list-style-type: none"> • Inflammatory bowel disease • Autoimmune chronic pancreatitis • Sjögren syndrome-associated chronic pancreatitis
Obstructive
<ul style="list-style-type: none"> • Pancreas divisum • Duct obstruction due to tumors
Miscellaneous
<ul style="list-style-type: none"> • Tropical pancreatitis • Fibrocalculous pancreatic diabetes • Postirradiation • Idiopathic.

Abbreviations: CFTR, cystic fibrosis transmembrane conductance regulator; SPINK1, serine protease inhibitor Kazal type 1.

without pancreatitis. Fecal elastase 1 (< 200 µg/g of stool) and MRCP are two noninvasive pancreatic function tests useful in this condition.

TREATMENT

Treatment depends upon the stage and etiology of chronic pancreatitis. It is similar to that of acute pancreatitis during the early phases characterized by discrete episodes. Intractable abdominal pain is the most distressing feature of CP. Treatment may be initiated with paracetamol, but most patients will ultimately require narcotics, resulting in the risk of narcotic addiction. Endoscopic, surgical and nerve block therapies have been tried in children with intractable pain.

Pancreatic enzyme supplementation helps restore digestive function as much as possible. Being proteins in nature, pancreatic enzymes may be destroyed by gastric HCl. This may be prevented to some extent by prescribing a proton pump inhibitor (PPI). Prolonged use of mega doses of pancreatic enzymes (> 6,000 units lipase/kg/meal) may culminate in a rare complication called *fibrosing colonopathy* resulting in formation of strictures in the ascending colon. Even though free radicals may play an important role in the pathophysiology of pancreatitis, the role of antioxidant therapy is still not clear. Another major problem is the development of diabetes as a sequel to destruction of the pancreatic islet cells.

TROPICAL PANCREATITIS

Tropical pancreatitis is a juvenile form of chronic calcific nonalcoholic pancreatitis prevalent almost exclusively in the developing countries of the tropics. In India, the highest prevalence is in the southeastern part of Kerala state. TP is almost exclusively seen in under-privileged children with severe PEM, associated with high levels of circulating free radicals which can damage the pancreas. The staple diet of these patients is cassava (*tapioca/Manihot esculenta*), a tuber rich in carbohydrates but very poor in proteins (0.4 g%) especially the sulfur containing amino acids methionine and cysteine. It contains toxic cyanogenic glycosides like linamarin and methyl linamarin (lotaustralin), which have been implicated in the pathogenesis of TP. Many recent studies have identified genetic markers especially mutations of SPINK1 and N34S.

Chronic severe abdominal pain in childhood, followed by diabetes in an emaciated teenager is the classic presentation. The radiologic demonstration of extensive pancreatic calcification clinches the diagnosis. Management includes control of diabetes with oral hypoglycemic agents and/or insulin. Long-term analgesics and surgery may be required for intractable pain.

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IN A NUTSHELL

1. Acute pancreatitis is relatively rare in children, but early diagnosis depends on strong clinical suspicion.
2. Infections, trauma and drugs are the most important predisposing factors.
3. Always exclude accidental/nonaccidental trauma in children with idiopathic recurrent pancreatitis.
4. Rule out HIV infection in children with unexplained pancreatitis as the disease as well as its treatment may result in pancreatitis.
5. There is no gold standard for the diagnosis of pancreatitis, but lipase and amylase are still useful laboratory markers.
6. In the diagnosis of pancreatitis, serum lipase is as sensitive but more specific than amylase.
7. Antimicrobials have no role unless patient has infected necrosis.
8. In recurrent pancreatitis, family history is important, since hereditary pancreatitis has an inherent propensity to lead onto carcinoma of the pancreas.
9. Early enteral feeding is of great importance; children should not be kept fasting for prolonged periods and nasogastric aspiration should be avoided.

Chapter 35.15

Practical Approach to Malabsorption

VS Sankaranarayanan

Maldigestion often occurs due to defect in the luminal phase of digestion of ingested food (defective hydrolysis of nutrients) secondary to insufficiency of exocrine pancreatic enzymes such as pancreatic amylase, lipase and bile salts, pancreatic trypsin and chymotrypsin, and small intestinal bacterial overgrowth (SIBO) due to surgical causes resulting in failure of mixed micelle formation for fat digestion.

Malabsorption occurs most often due to defective mucosal absorption like celiac disease, cow's milk protein allergy (CMPA), tropical sprue, etc. It is characterized by relatively less fat in stool (absence of grease/oil) and presence of abdominal bloating/flatulence, anemia and hypoalbuminemia. A good history and physical examination of the patient will give clue to the etiology and clinical diagnosis of malabsorption.

HISTORY

Consanguinity Abetalipoproteinemia, cystic fibrosis, congenital intestinal defects.

Age of onset Diseases causing malabsorption can present insidiously at different age groups (e.g., congenital disorders like cystic fibrosis, primary lactase deficiency at birth, acrodermatitis enteropathica and celiac disease by weaning age). Family history of similar illness has a role in cystic fibrosis, Crohn's disease, abetalipoproteinemia and food allergy.

Stool history Duration of chronic diarrhea, character, frequency, volume, consistency of stools, presence or absence of blood, mucus [inflammatory bowel disease (IBD)], oily or greasy, soft, bulky, pale and rancid stools (exocrine pancreatic insufficiency, biliary disease) or explosive with sore bottom (lactose malabsorption); diarrhea after gluten containing diet (celiac disease) or cow's milk (CMPA); associated symptoms like abdominal pain (Crohn's disease, pancreatic or biliary disease) failure to thrive and (fat, protein or carbohydrate malabsorption) nutrient deficiency like pallor and anemia (iron deficiency) glossitis and cheilitis (vitamin B complex especially, folic and B₁₂ deficiency) angular stomatitis and cheilitis (riboflavin deficiency), edema (protein deficiency), stunting of growth with bony abnormalities (rickets), bleeding gums (vitamin C deficiency) epistaxis and petechiae (vitamin K deficiency) perioral and perianogenital ulcerations with alopecia (zinc deficiency—acrodermatitis enteropathica).

Abdominal surgery will suggest small bowel bacterial overgrowth or short gut syndrome or adhesive obstruction.

Immune deficiency History of contact with human immunodeficiency virus (HIV), or history of organ transplantation, chronic recurrent infections (tuberculosis, congenital immune deficiency) and drugs causing malabsorption (anticonvulsants).

Dietetic history Early introduction of cow's milk in CMPA, cereals in weaning food—wheat, rye, barley, oats in celiac disease. Appetite is often increased in exocrine pancreatic insufficiency and decreased in celiac disease.

PHYSICAL EXAMINATION

Physical examination includes a systematic general examination and systemic examination with assessment and recording of growth of the child. Any drop in growth centiles clinically will manifest as malnutrition and growth stunting (an indicator of chronic malabsorption). The attending physician is expected to look for hydration status; nutritional status [grade of protein energy malnutrition (PEM), stunting, vitamin, trace elements and mineral deficiencies]; presence/absence of peripheral edema (protein deficiency); constitutional symptoms such as fever (infection or inflammation); extra gut manifestations in eyes like Bitot spots; skin (infection, dermatosis, rash, edema, surgical scar, joint swelling in autoimmune diseases, and oral cavity (stomatoglossitis); perianal area for excoriation, fistulae, fissures (Crohn's disease); persistent thrush in HIV; and abdominal examination for distension, scar, masses, organomegaly and ascites.

In summary, the physician at this stage should approach any child with malabsorption with high degree of clinical suspicion and try to answer the following questions: whether the patient is having chronic diarrhea of small bowel or large bowel; if small bowel, whether secretory or osmotic or mixed; if large bowel, whether it is inflammatory or infective or infiltrative; whether the child has maldigestion or malabsorption. What are the consequences of the disorder and how serious? And also determine the attitude of the caretaker and affordability for battery of laboratory diagnostic investigations to assess the specific cause. Only then a long-term management, counseling, and follow-up can be planned in an effective manner.

INVESTIGATIONS

Confirmation of malabsorption is based on the relevant laboratory tests (**Table 1**). Various laboratory investigations intended for chronic diarrhea hold good for malabsorption with chronic diarrhea also. These will be discussed in detail in the next section on diarrheal disorders.

The cause for malabsorption can be determined by the following tests: endoscopy (scalloping for atopy, white plaques in lymphagiectasia, eosinophilic abscesses, duplication cysts, aphthoid ulcers in Crohn's disease); small intestinal biopsy for villi/crypt study, parasites, eosinophil count (> 15/HPF); colonoscopy and biopsy (for tuberculosis, IBD, CMPA) and CT scan. The specific diagnostic tests for etiology of malabsorption include celiac serology [endomysial antibody, immunoglobulin A (IgA) tissue transglutaminase]; sweat chloride test and mutation analysis (cystic fibrosis); cow's milk specific IgE antibody (IgE specific CMPA), among others. Upper gastrointestinal endoscopy and duodenal biopsy are the mainstay of confirmatory diagnosis of malabsorption (**Table 2**).

If pancreatic disease with secretory insufficiency is suspected, consider tests for secretory function, e.g., elastase or chymotrypsin in stool; and CT/MRI of pancreatic duct-systems or ERCP. The gold standard still is the secretin-pancreozymin test; this test is

Table 1 Clinical and laboratory findings in malabsorption

<i>Signs and symptoms</i>	<i>Laboratory findings</i>	<i>Malabsorbed nutrient</i>
Diarrhea	Stool weight ↑, serum potassium ↓	Water, electrolytes
Steatorrhea	Fecal fat ↑, serum cholesterol ↓	Dietary lipids, bile acids
Weight loss	Fecal fat ↑, fecal chymotrypsin or elastase ↓, xylose test ↓	Fat, carbohydrates, protein
Anemia	Serum iron ↓, hypochromic, microcytic, RDW ↑	Iron
Pernicious anemia, glossitis, Knuckle pigmentation	Macrocytic blood picture, megaloblastic marrow, Schilling's test abnormal	Vitamin B ₁₂ , folic acid
Pain in limbs and bones, pathologic bone fractures, Chvostek sign	Serum calcium ↓, alkaline phosphatase ↑	Potassium, magnesium, calcium, vitamin D ₃ , protein, amino acids
Signs of bleeding, easy bruising, petechial hemorrhage	Prothrombin time ↑	Vitamin K, vitamin C
Edema	Total protein ↓, serum albumin ↓, fecal α1-antitrypsin clearance ↑	Protein
Abdominal distension, gas	Abdominal X-ray, sonography, glucose H ₂ -breath test	Carbohydrates
Lactose intolerance (explosive diarrhea)	Lactose H ₂ -breath test ↑ intestinal mucosal lactase ↓	Lactose
Peripheral neuropathy		Vitamins B ₁ , B ₆ , B ₁₂
Hyperkeratosis, parakeratosis, acrodermatitis	Retinol, zinc serum levels ↓	Vitamin A, zinc
Night blindness	Serum retinol ↓	Vitamin A
Malabsorption-clinical	Lymphocytopenia	Lymphangiectasia
Younger age, chronic diarrhea, Abetalipoproteinemia	Acanthocytes in blood smear	Calorie deficiency, deficiency of essential nutrients
Suspected Crohn's disease, tuberculosis	ESR ↑	Essential nutrients, calorie deficiency

Abbreviations: RDW, red cell distribution width; ESR, erythrocyte sedimentation rate.

Table 2 Diagnostic significance of small bowel mucosal biopsy for malabsorption

<i>Always positive</i>	<i>Diagnostic and patchy</i>	<i>Diagnostic but nonspecific (abnormal villus atrophy)</i>
<ul style="list-style-type: none"> Abetalipoproteinemia (intraepithelial fat) Whipple disease (acid fast organism) Agammaglobulinemia (absent plasma cells in LP) 	<ul style="list-style-type: none"> Lymphangiectasia (dilated lacteals in LP) Giardiasis Strongyloidiasis Lymphoma Eosinophilic gastroenteritis (> 15 eosinophils/hpf) Crohn's disease (noncaseating granuloma), etc. 	<ul style="list-style-type: none"> Celiac disease Tropical sprue Cow's milk protein allergy Severe PEM Prolonged iron and folate deficiency

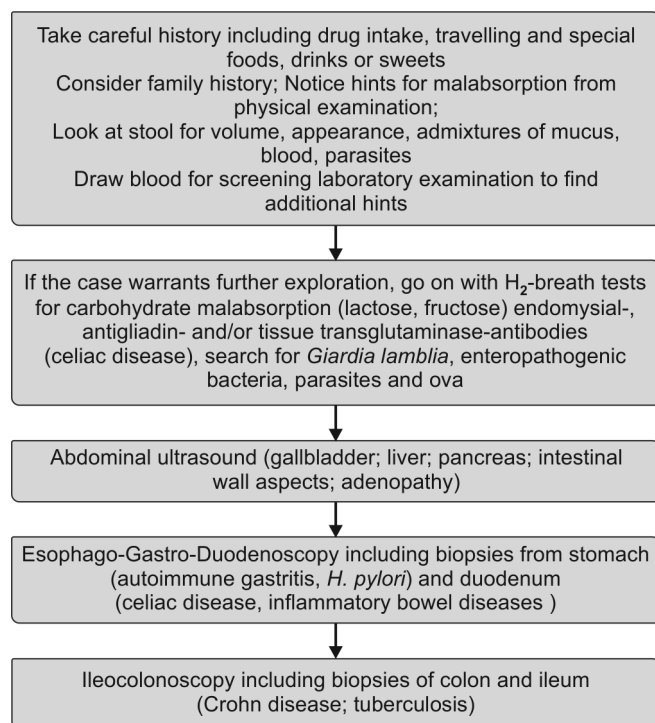
Abbreviations: LP, lamina propria; PEM, protein energy malnutrition.

not really necessary for routine examination but may be helpful in individual cases; likewise the quantitative determination of 72 hour fecal fat excretion is cumbersome and not done now. When in doubt a therapeutic trial with pancreatic enzyme supplementation may be considered. If small bowel disease is still within the differential diagnostic scope, consider: Schilling-test (Vitamin B₁₂ malabsorption), Glucose-H₂ breath test (bacterial overgrowth), α1-antitrypsin clearance (protein losing enteropathy), small bowel X-ray (fistulae, diverticula, blind loops, short bowel, etc.), and angiography of celiac and mesenteric arteries (ischemic bowel damage).

Flow chart 1 presents an algorithm for diagnosis of malabsorption syndrome.

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Flow chart 1 An algorithm for diagnosis of malabsorption syndrome

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IN A NUTSHELL

1. Maldigestion and malabsorption describe insufficient nutrient uptake and utilization by the gastrointestinal tract.
2. The etiology is varied with wide spectrum of clinical signs, symptoms and biochemical findings including vitamin and nutrient deficiency syndromes.
3. Chronic diarrhea and failure to thrive are the most common presenting symptom, yet there are several other presentations.
4. It is emphasized that the attending physician should focus on the underlying disease entity to provide appropriate counseling and treatment after making the diagnosis of a malabsorption syndrome.

Chapter 35.16

Specific Malabsorption Syndromes

Srinivas S

Malabsorption syndromes refer to disorders in the intestinal processes of digestion and/or transport one or more nutrients—*carbohydrate, fat, protein or micronutrients* across the intestinal mucosa into the systemic circulation. This could be either due to a congenital disorder or a secondarily acquired disorder. **Table 1** enlists the common causes of malabsorption syndrome in India. In this chapter we will discuss some causes of malabsorption which are not discussed elsewhere in this book. Readers are also advised to refer to the chapters on chronic diarrhea, celiac disease, inflammatory bowel diseases (IBD), cystic fibrosis and alpha-1-antitrypsin deficiency.

SHORT BOWEL SYNDROME

Most patients with short bowel syndrome (SBS) have undergone bowel resection for one of the following:

- A congenital anomaly such as an omphalocele, gastroschisis, or intestinal atresia
- Necrotizing enterocolitis associated with prematurity
- Intestinal ischemia from malrotation and volvulus
- Crohn's disease (infrequent with current treatment)
- Total colonic aganglionosis.

Pathogenesis In general, virtually all digestion and absorption are completed within the first 100–150 cm of jejunum in a healthy individual. In the absence of an intact colon, the minimum length of healthy bowel necessary to avoid parenteral nutrition is approximately 100 cm. Patients who have less than 100 cm of jejunum exhibit significant malabsorption.

Table 1 Etiology of malabsorption in India

Pathology	Specific diseases
• Short gut syndrome	<i>Due to surgical intestinal resection for bowel gangrene as in</i> <ul style="list-style-type: none"> • Neonatal necrotizing enterocolitis • Intussusception • Malrotation and volvulus
• Damage to mucosal villi	<ul style="list-style-type: none"> • Celiac disease • Rotaviral diarrhea • Food protein enterocolitis, e.g., CMPA • Persistent diarrhea • Crohn's disease • Tuberculosis • Immunodeficiency state—with recurrent infections including giardiasis/strongyloidiasis • Radiation/chemotherapy/GVHD
• Pancreatic insufficiency	<ul style="list-style-type: none"> • Chronic pancreatitis • Cystic fibrosis
• Reduced intraduodenal bile causing fat malabsorption	<ul style="list-style-type: none"> • Cholestatic liver disorders
• Lymphatic disorders/disorders to lymph flow often manifesting as protein losing enteropathy	<ul style="list-style-type: none"> • Lymphangiectasia • Constrictive pericarditis

Abbreviations: CMPA, Cows' milk protein allergy; GVHD, graft-versus-host disease.

Clinical features Children with SBS may present with various medical issues, depending on the extent of their bowel resection, presence/absence of ileocecal valve and the level of medical complexity like total parenteral nutrition (TPN) dependency. These may include failure to thrive (FTT), nutritional deficiencies, malabsorptive diarrhea, recurrent dehydration, need for specialized enteral formula, catheter-related infections or sepsis.

Malabsorption of various nutrients also is likely to occur depending upon the area of bowel resected. For example, extensive jejunal resection leads to carbohydrate malabsorption. The undigested foods produce an osmotic diarrhea typical of most patients with SBS. The proximal small bowel is also important in the absorption of proteins, fat, and certain micronutrients, including copper. Semi-elemental or pre-digested formula is hence better tolerated than normal formula in short gut syndrome. Extensive terminal ileal resection would result in vitamin B₁₂ deficiency and bile salt malabsorption causing cholestatic diarrhea.

Management The management of SBS requires an aggressive multidisciplinary approach. Since loss of intestinal mucosal absorptive surface remains the major hurdle, the main issues during the initial months following resection would be loss of fluid and electrolytes causing dyselectrolytemia and dehydration. The institution of early and aggressive enteral therapy is the most important stimulus for intestinal adaptation and the eventual discontinuation of parenteral therapy. Aggressive resuscitation with fluids, parenteral nutrition, or both is often required in the 1st week after intestinal resection. The hypersecretion of HCl noted within the first 12 months postresection is usually treated with H₂ blockers or proton pump inhibitors. Cholestyramine has been used to bind bile salts in patients with cholestatic diarrhea.

Prognosis Over a period time (months to years) intestinal adaptation occurs and diarrhea is no longer a problem in children with SBS; though some children with extensive bowel resections remain partially/completely TPN dependent for life. The ileum has greater adaptive function as far as improving its absorptive function in the presence of SBS. Small-bowel transplantation is used only if absolutely necessary in patients with associated severe advanced liver disease and those with major vascular access problems.

LACTOSE INTOLERANCE

Lactose intolerance is a syndrome characterized by impaired digestion of a disaccharide-lactose. This could be a congenital (primary lactose intolerance) or acquired (secondary lactose intolerance). The congenital variety is extremely rare.

Primary lactose intolerance due to congenital lactase deficiency is an extremely rare condition which presents with diarrhea since birth. The diarrhea typically is profuse while breastfed and stops while the child is put on a nonlactose containing formula. This is a permanent deficiency of lactase enzyme and does not improve with time.

In contrast secondary lactose intolerance is much more common and is often transient. Virtually any condition which causes intestinal mucosal damage can cause secondary lactose intolerance. This is because the *lactase* is present in the tips of the intestinal villi and is often the first among the intestinal disaccharidases to be lost in the event of mucosal injury.

Etiology The most common cause of transient secondary lactose intolerance is a viral gastroenteritis—like rotaviral diarrhea. Other causes include celiac disease, CMPA, Crohn's disease, radiation enteritis, GVHD, etc. Secondary lactase deficiency due to intestinal mucosal injury can appear at any age. However, children below 2 years are more susceptible because of many factors, including a high sensitivity of the gut to infectious agents, low reserve because of the small intestinal surface area, and high reliance on milk-based products for nutrition. Adult-onset lactase deficiency is more of a

genetically determined condition. Asians are known to be more prone for lactase deficiency than Caucasians.

Clinical features Symptoms are more severe in infants and younger children because of many factors, including a high sensitivity of the gut to infectious agents, low reserve because of the small intestinal surface area, and high reliance on milk-based products for nutrition. These include abdominal distension, borborygmi and a profuse watery diarrhea following ingestion of milk often causing perianal excoriation in infants and young children. Stool pH less than 5.5 along with the presence of stool reducing substance greater than or equal to 2+ (yellow) aids in the diagnosis. It is important to test the liquid component of stool for reducing substance. The clinical features in older children are less severe and restricted to flatulence, abdominal discomfort/crampy pain and the occasional diarrhea. A lactose hydrogen breath test is used for the diagnosis of lactose intolerance in older children.

Management Lactose intolerance is easily managed by reducing or completely avoiding lactose containing foods. Alternative non-lactose milk formula like soymilk is well tolerated. The secondary lactose intolerance improves within a few weeks once the primary disease causing intestinal damage is treated adequately and the intestinal villi recover.

PANCREATIC EXOCRINE INSUFFICIENCY

This is infrequently seen in chronic pancreatitis and invariably seen in cystic fibrosis in children. The classical clinical manifestation is steatorrhea described as the passage of large volume, foul smelling and greasy stools. This is seldom confused with chronic diarrhea and almost never needs intravenous fluid rehydration. The classical history is that of a hungry child who eats a lot and still does not grow well due to passage of large volume stools—occasionally oily. Traditionally the confirmation of pancreatic exocrine insufficiency requires a 72 hours fecal fat estimation. This is very cumbersome and is not routinely used except in select laboratories in the world. Early pancreatic exocrine insufficiency may manifest only as failure to thrive and estimating fecal elastase is useful method to confirm the same. In general as the conventional Indian diet tends to be low in fat when compared to the Western diet, clinically apparent steatorrhea does not manifest until later.

Management of pancreatic steatorrhea includes supplementing the patient's diet with oral pancreatic lipase enzyme as capsules. Pancreatic lipase capsules have to be given along with every meal with higher doses being needed for fat rich meals. Doses as high as 2,500 lipase units/kg/day are used in infants with cystic fibrosis without any complications.

MALABSORPTION IN CHOLESTATIC DISORDERS

The classical example of this syndrome is a child with neonatal cholestasis syndrome presenting with an intracranial bleed secondary to late hemorrhagic disease of newborn, i.e., secondary to vitamin K malabsorption.

The fat soluble vitamins A, D, E and K depend on bile acids for their absorption. Hence, the lack of intraduodenal bile in neonatal cholestatic disorders predisposes to fat soluble vitamin deficiency. Malabsorption of fat soluble vitamins increases with severity of cholestasis. Infants with prolonged cholestasis of infancy like Watson Alagille syndrome or progressive familial intrahepatic cholestasis are likely to develop Bitot's spots unless given regular parenteral vitamin A supplements. Children with cholestatic disorders should be given vitamin K, A and D injections regularly.

Dietary fat is broken down by pancreatic lipase into predominantly long-chain fatty acids and they are dependent on bile acids for micelle formation and absorption. In cholestasis, due to the lack of intraduodenal bile acids, fat is malabsorbed and this

results in the passage of greasy/oily stools (steatorrhea). Unlike in pancreatic steatorrhea, exocrine pancreatic lipase enzyme supplementation will not improve the malabsorption. Substitution of medium-chain triglycerides (MCT) in the diet in place of long-chain fatty acids improves steatorrhea and weight gain as MCT does not require bile acids/micelle formation for its absorption. This forms the basis for prescribing a formula rich in median chain triglycerides for young infants with cholestasis. Coconut oil is a naturally rich source of MCT and should be used in their diet.

PROTEIN LOSING ENTEROPATHY: INTESTINAL LYMPHANGIECTASIA

Protein losing enteropathy is a general term used to describe all conditions that cause loss of proteins through the gastrointestinal tract. For practical purposes the diseases causing protein losing enteropathy can be grouped into the following categories:

- Bad mucosal disease with ulcerations and erosions causing loss of protein, e.g., IBD, intestinal tuberculosis, GVHD, CMPA or
- Conditions causing lymphatic block, e.g., primary intestinal lymphangiectasia (PIL), constrictive pericarditis, post-Fontan procedure.

Primary intestinal lymphangiectasia This is a unique condition manifesting as a protein losing enteropathy where the lymphatic channels in the intestines are congenitally and abnormally dilated (ectatic).

Pathophysiology These abnormally dilated lymph channels have some form of functional block to lymph flow. A fat rich meal is often the best stimulus for lymph flow as this causes the ectatic channels to swell up and burst open thus discharging/leaking lymph into the intestines. As lymph is a rich source of proteins and immunoglobulins, this results in protein losing enteropathy.

Clinical manifestations Patients with primary intestinal lymphangiectasia usually present in childhood with edema and diarrhea (malabsorption and steatorrhea). Edema may be unilateral or bilateral, depending on the site of the lesion. Edema in primary intestinal lymphangiectasia is usually bilateral, while the secondary type often manifests as unilateral edema and is caused by various neoplastic, infiltrative, and inflammatory lesions affecting one side of the body. Frequently, lymphocytopenia and hypogammaglobulinemia are present, though the absence of these does not exclude intestinal lymphangiectasia.

Upper gastrointestinal (GI) endoscopy may occasionally reveal a starry sky pattern of the duodenal mucosa due to dilated intestinal lacteals and biopsies may reveal dilated intestinal lacteals consistent with the diagnosis of PIL.

Complications Despite hypogammaglobulinemia, opportunistic infections rarely occur, although lymphocytopenia predisposes patients to abnormal cellular immunities, including homograft rejection and cutaneous anergy. In patients with early onset PIL, growth retardation is common. The risk of lymphoma is increased in PIL. Fibrotic entrapment of the small bowel is reported in patients with congenital intestinal lymphangiectasia. Oral manifestations include gingivitis caused by poor lymphocytic function and enamel defects caused by poor calcium absorption.

Management Dietary modifications include a low-fat diet and substitution of long-chain fatty acids with MCT. MCTs do not stimulate lymph flow and are directly absorbed into the circulation without micelle formation. This strategy thus reduces the lymph leak/protein loss into the intestines.

Clinical course and response are highly variable depending upon the extent and severity of intestinal lymphangiectasia and whether it is part of a syndrome involving abnormal lymphatics throughout the body; e.g., Hennekam syndrome carries a poor

prognosis. Medications are not usually useful in intestinal lymphangiectasia. Treatment of secondary causes of lymphangiectasia targets the underlying disease. Octreotide is found to be effective in refractory cases.

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IN A NUTSHELL

1. Calcium, vitamin D, iron and folic acid are absorbed in proximal small intestine while bile acids and vitamin B₁₂ are absorbed in terminal ileum.
2. Virtually any disease process causing intestinal mucosal villi damage can cause a secondary lactose intolerance which improves with intestinal villi recovery.
3. Patients with a short bowel and an intact ileum and colon rarely need long-term enteral or parenteral nutrition.
4. Celiac disease needs to be treated with lifelong adherence to gluten-free diet.
5. Pancreatic steatorrhea can be effectively treated with exocrine pancreatic enzyme supplementation.
6. Children with neonatal cholestasis are prone for fat soluble vitamin deficiency—which if not treated in time can result in intracranial bleed/night blindness.
7. Intestinal lymphangiectasia is a congenital cause of protein losing enteropathy which is managed with diet rich in MCT.

Chapter 35.17

Inflammatory Bowel Disease

Rishi Bolia, Anshu Srivastava

The term *inflammatory bowel disease (IBD)* denotes a group of disorders characterized by chronic intestinal inflammation. It includes Crohn's disease (CD), ulcerative colitis (UC) and inflammatory bowel disease unclassified (IBDU).

Ulcerative colitis, the first to be described in 1859, is localized to the colon and spares the rest of the gastrointestinal (GI) tract. The disease begins in the rectum and extends proximally for a variable distance and is limited to the colonic mucosa. CD, which was first described as *regional ileitis* in 1932, can involve any region of the alimentary tract from the mouth to the anus and leads to transmural inflammation. Although there is an overlap between the two disorders, they differ significantly in their clinical course, management and outcome. Around 10% of patients with isolated colonic involvement have some features of both UC and CD, and are labeled as IBDU at diagnosis. These cases may show typical UC or CD features on follow-up. The term *indeterminate colitis* is used when the diagnosis of CD or UC cannot be made even on the histology of a colectomy sample.

EPIDEMIOLOGY

Inflammatory bowel disease has been most prevalent in North America, Northern Europe and the United Kingdom. The prevalence varies not only by the geographic location, but also by race and ethnicity. Pediatric IBD accounts for about 20–25% of all cases of IBD in the west and 7% of all cases in the available data from India. Overall, CD is more common than UC with a slightly higher prevalence in boys than girls. Most cases present between 10 years and 14 years of age. About 10% of all pediatric IBD occurs in children less than 6 years of age and 1% in infants. Children with UC have a more extensive colonic involvement at presentation and a higher propensity for extension of the disease compared to adults. In CD, children have more colonic and perianal disease and less of isolated small bowel involvement in comparison to adults.

The risk of IBD in family members of an affected person is around 7–30% and a child in whom both parents have IBD has a 33% chance of developing the disease. Although it is more common to have the same type (UC/CD) of IBD in family members, both CD and UC have been reported in the same family. A concordance rate of approximately 50% has been observed amongst monozygotic twins for all types of IBD.

ETIOPATHOGENESIS AND GENETICS

The etiopathogenesis of IBD is multifactorial. There is a complex interplay of genetic factors, environmental triggers and gut microflora which initiates an abnormal mucosal immune response and leads to intestinal inflammation. When the normal body mechanisms that keep *physiologic* inflammation in check fail, then pathologic inflammation ensues. But whether this represents an abnormal response to normal enteric antigens or a normal response to an as-yet-unidentified microbe is not known. Inflammatory mediators (cytokines, arachidonic acid metabolites, reactive oxygen metabolites and growth factors) are involved, with overproduction of proinflammatory cytokines and underproduction of anti-inflammatory or regulatory cytokines, leading to destruction of the tissue and remodeling with fibrosis.

Ulcerative colitis A number of environmental factors have been postulated to be important and may influence the development of

UC. Appendectomy, a diet low in refined sugars, breastfeeding and smoking are considered protective. Psychological stress and nonsteroidal anti-inflammatory drugs (NSAIDs) are potential triggers. The intestinal microbiome of IBD patients (both UC and CD) differs from that of healthy controls. Genome wide association study has shown that IBD is a complex disorder, with some shared and many unique predisposing genes between CD and UC. About 47 susceptibility loci/genes for UC alone and another 28 for both UC and CD are known. Linkage studies have shown that there are susceptibility genes for UC on chromosome 1, 2, 3, 5, 6, 7, 10, 12 and 17. The *IBD2* locus on chromosome 12 is the most common.

Crohn's disease A number of environmental factors such as gut microflora, *westernized* diet [rich in refined sugars and n-6 polyunsaturated fatty acids (PUFAs)], lack of breastfeeding and presence of infectious agents such as *measles* and *Mycobacterium paratuberculosis* have been implicated. Smoking and oral contraceptives appears to predispose to CD. Genome wide association study has shown 71 susceptibility loci/genes for CD. Mutations in *NOD2/CARD15* gene, located in pericentromeric region of chromosome 16, significantly increase the risk of CD and this is particularly associated with ileal location, younger age of disease onset and penetrating disease phenotype. Recently two new pathways have been implicated, which includes T-cell regulation by the IL-23 pathway and the process of autophagy which controls intracellular bacteria by the *ATG16L1* and *IRGM* gene. Mutations in IL-10 and IL-10R pathway have also been identified, especially in children with infantile onset of the disease. This subgroup of infantile IBD is characterized by severe disease, lack of response to the standard IBD therapy and poor outcome.

In CD, the main abnormality is in defective recognition and processing of intracellular bacteria whereas in UC it is of intestinal barrier integrity and function. However, it is important to remember that genetic factors provide no direct bearing on therapy.

CLINICAL PRESENTATION

Ulcerative colitis Passage of loose stools with blood and mucus accompanied by tenesmus and urgency is the most common presentation in children. In majority of cases, symptoms have a slow and insidious onset. Systemic symptoms such as anorexia, weight loss, fever and abdominal pain are present in those with extensive disease. The abdominal pain is crampy in nature and occurs before passage of stools. Fecal incontinence may be seen in patients with severe proctitis. A small percentage of children have an initial fulminant presentation with greater than five bloody stools/day, fever, tachycardia, anemia and abdominal tenderness and known as acute severe colitis. These children are at risk of developing the complication of toxic megacolon (presence of dilated colonic loop greater than 5.5 cm on abdominal X-ray) and perforation.

Crohn's disease The various sites of disease (small bowel, colon and gastroduodenal), discontinuous lesions and progression to involve other bowel segments with time lead to varied clinical manifestations in CD. This is also responsible for the delay in diagnosis of these subjects. Diarrhea, abdominal pain and weight loss are the classical triad of CD, but only 25% of affected children have this typical presentation. Abdominal pain is the most common presenting symptom (72%), followed by diarrhea (56%), weight loss (58%), lethargy (25%), anorexia (27%) and poor growth. Patients with predominant colonic disease present as diarrhea with blood and mucus, while those with small bowel involvement manifest as abdominal pain, watery diarrhea or with features of subacute intestinal obstruction. Some children may present with perianal disease in the form of fissures, fistulas and abscesses (**Fig. 1**). Growth failure in CD may precede the abdominal complaints by few months and is characterized by delayed skeletal maturation,



Figure 1 Perianal fistula (marked with black arrow) and fissure (short white arrow) along with rash in a child with Crohn's disease

reduced lean body mass and delayed puberty. Early satiety, nausea, vomiting and epigastric pain may be seen in patients with gastroduodenal CD. Esophageal involvement is very uncommon and leads to dysphagia and odynophagia.

Extraintestinal Manifestations

Extraintestinal manifestations (EIM) of IBD are present at diagnosis in 6–28% cases. Musculoskeletal (arthralgia, arthritis, and sacroiliitis) complaints are the most common EIM seen in 20–25% cases. Other EIM include aphthous stomatitis, pyoderma gangrenosum, erythema nodosum (EN), uveitis, scleritis, primary sclerosing cholangitis (PSC), fatty liver, autoimmune hepatitis and autoimmune hemolytic anemia. They may be present before, during or after the development of intestinal symptoms. EIM are more frequent in subjects with moderate to severe disease as compared to those with mild disease. Amongst the various EIM, PSC is more common in UC while ankylosing spondylitis (AS) and EN are more often seen in CD than UC cases.

Some EIMs, such as peripheral arthritis and EN correlate with disease activity whereas PSC, AS, and sacroiliitis do not. Arthritis in IBD is of two types: (1) peripheral arthritis involving primarily large joints, which may be further subclassified as pauciarticular (< five joints) or polyarticular (\geq five joints), and (2) axial arthropathy which includes AS and sacroiliitis.

Examination Complete physical examination with weight and height monitoring at each visit to detect growth faltering is essential in all children with IBD. Anemia, clubbing and pedal edema due to hypoalbuminemia may be present in patients with moderate to severe disease. Abdominal distension, loss of bowel sounds and rebound tenderness suggest presence of toxic megacolon. Patients with ileocolonic CD may have a mass palpable in right iliac fossa. Perianal examination may show presence of fleshy anal tags, deep fissures, abscesses and fistulae in children with CD. Presence of hepatosplenomegaly with or without jaundice points towards liver disease like sclerosing cholangitis.

DIAGNOSIS

As a result of its varied presentation, diagnosis of IBD is often delayed by 5–15 months, with UC being diagnosed earlier than CD due to the alarming symptom of blood in the stools. The IBD working group of the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), published *The Porto*

Criteria for the diagnosis of childhood IBD. These criteria require that diagnosis of IBD should be based on a combination of history, physical examination, laboratory evaluation, esophagogastroduodenoscopy (EGD) and ileocolonoscopy with histology and imaging of the small bowel.

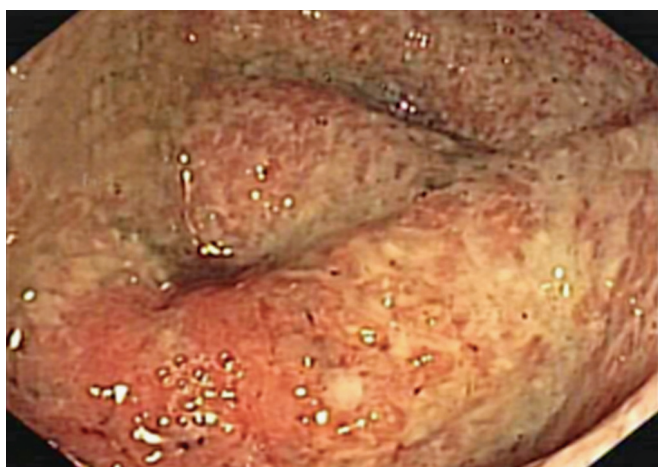
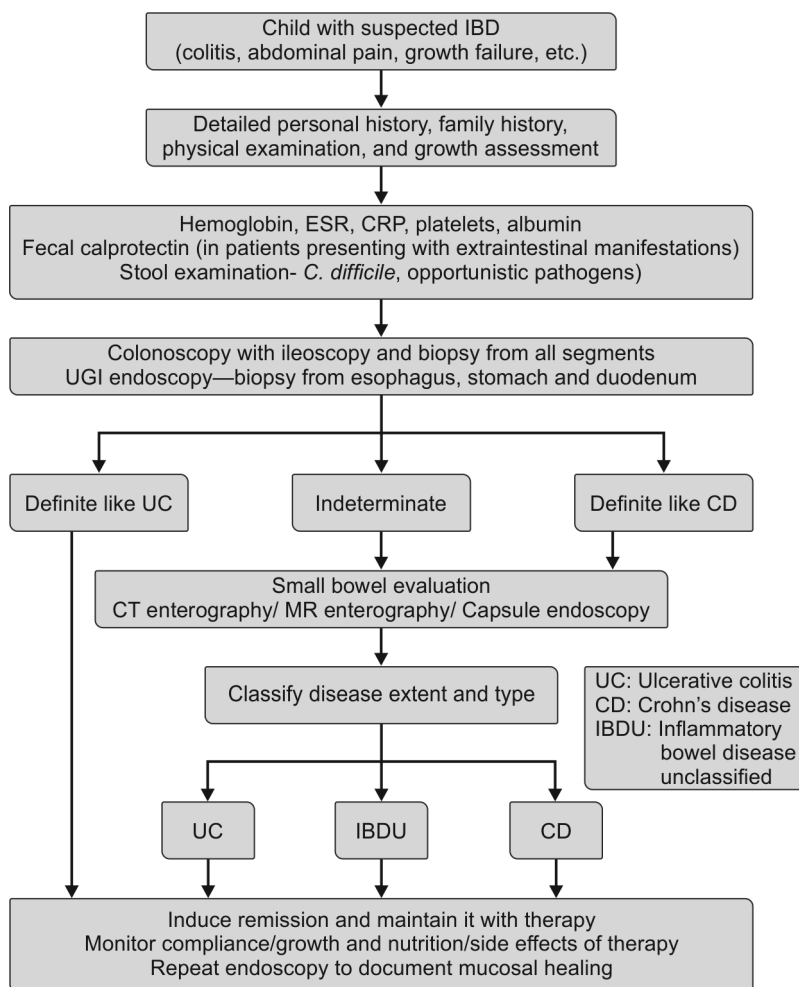
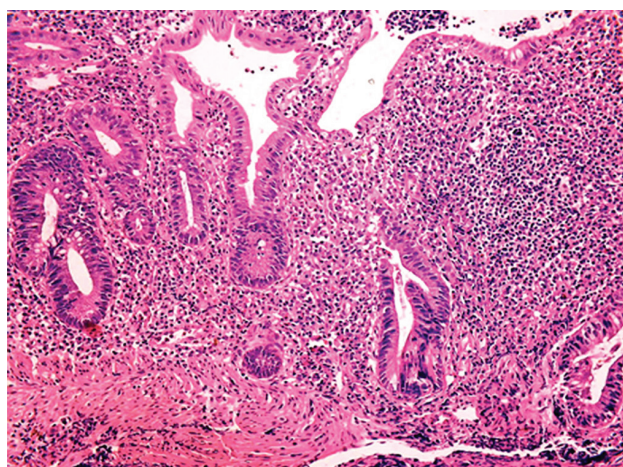
The stepwise evaluation of a child with suspected IBD is shown in **Flow chart 1**. Initial blood tests should include complete blood count, inflammatory markers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), serum albumin, transaminases and gamma-glutamyl transpeptidase (GGT). In a patient with active disease, there is anemia, hypoalbuminemia, thrombocytosis with raised ESR and CRP. However, normal values may be seen in patients with mild or inactive disease and thus do not exclude IBD.

Calprotectin is a protein, accounting for 30–40% of a neutrophil's cytosol. For the detection of intestinal inflammation fecal calprotectin (FC) is superior to any blood test. However, it is a nonspecific marker of inflammation and elevated FC levels cannot distinguish between the different causes of inflammation (e.g., IBD vs infection) or location of the disease (small vs large bowel). It is useful to discriminate between abdominal pain of functional origin and that due to inflammatory lesion of CD. Extraintestinal disease such as uveitis and PSC should be screened for by an ophthalmic examination and liver function tests (transaminases and GGT).

Various serological tests like antisaccharomyces cerevisiae antibody (ASCA) and perinuclear-antineutrophil antibody (p-ANCA) have been used for diagnosis and subtyping of IBD. ASCA is found more often in CD (50–70%) than in UC (10–15%) and p-ANCA is more common in UC (60–70%) than in CD (20–25%). However, they have a poor sensitivity and specificity and thus not very useful in clinical practice. Presence of ASCA also does not help in differentiating CD from colonic tuberculosis (TB).

Ileocolonoscopy and EGD should be done as the initial work-up for all children with suspected IBD. It is important that multiple biopsies are obtained from all areas of the visualized GI tract, even when macroscopic lesions are absent. The findings on endoscopy should be well documented. The typical macroscopic features of UC include erythema, granularity, friability, and superficial small ulcers which start from the rectum and extend proximally to various levels (**Fig. 2**). As per the Paris Classification, UC is labeled as proctitis (rectum only), left-sided (distal to splenic flexure), extensive (distal to hepatic flexure) and pancolitis, depending upon the extent of colonic involvement. Pancolitis is the most common type in children, seen in 43–90% cases of UC. At times, the distal 5–10 cm of the terminal ileum may show erythema and/or edema without any ulceration and stricture in patients with pancolitis and this is known as *backwash ileitis*. Colonic histology shows cryptitis and crypt abscess along with signs of chronicity, i.e., alteration of the crypt architecture (crypt loss, branching), basal plasmacytosis and paneth cell metaplasia (**Fig. 3**).

Crohn's disease is characterized by the presence of noncontiguous aphthous or linear deep ulcers involving single or multiple segments of the colon (**Fig. 4**). The terminal ileum may show aphthous or linear ulcers with or without luminal narrowing. Histologically the disease is characterized by chronic focal inflammation, signs of activity (crypt abscess/cryptitis) and noncaseating granulomas (**Fig. 5**). The Paris classification is used for defining the disease extent and nature. It gives an account of the age of onset, disease location (ileal alone, colonic, ileocolonic, isolated upper GI), behavior (stricturing/penetrating/inflammatory) and effect on growth at a glance. Ileocolonic disease is most commonly seen in children with CD. The differentiating features between CD and UC have been summed up in **Table 1**. In some cases, despite all efforts, it may not be possible to confidently diagnose patients as UC or CD so they are best labeled as IBDU.

Flow chart 1 Algorithm for diagnosis of pediatric inflammatory bowel disease (IBD)**Figure 2** Colonoscopy showing diffuse ulceration, erythema, loss of vascular pattern and edema in a patient with ulcerative colitis**Figure 3** Rectal biopsy section from a case of active ulcerative colitis shows crypt distortion, crypt loss, crypt branching and mucodepletion and dense mixed inflammatory cell infiltrate in lamina propria. (HE X 200 original magnification)

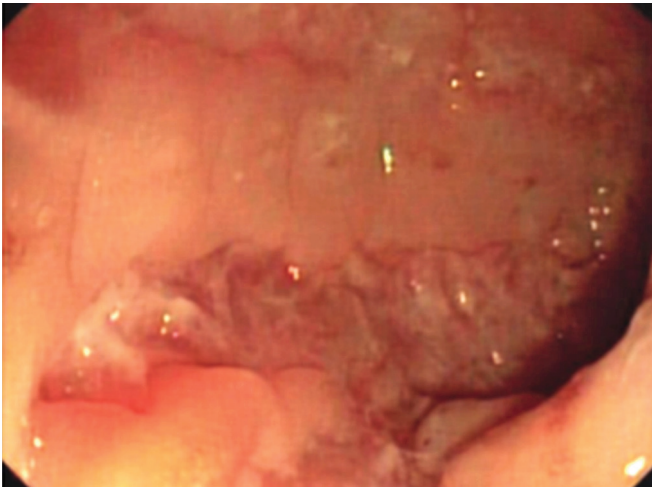


Figure 4 Colonoscopy showing deep longitudinal ulcers in a patient with Crohn's disease

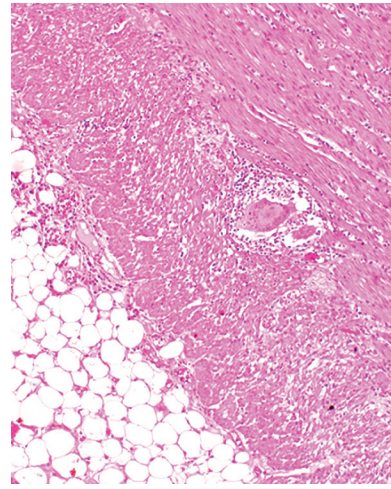


Figure 5 Sections from right-sided colectomy specimen shows granuloma in muscularis propria near adventitial adipose tissue from a case of Crohn's disease. (HE X 100 original magnification)

Table 1 Differences between Crohn's disease and ulcerative colitis

	<i>Crohn's disease</i>	<i>Ulcerative colitis</i>
Abdominal pain	+++	±
Bleed per rectum	++	++++
Growth failure	++	±
Weight loss	++	±
Perianal disease	+++	—
Rectal sparing	++	Rare
Small bowel disease	Common	None except backwash ileitis
Strictures	++	Rare
Fistulas	++	—
Colonoscopy	Aphthous, deep linear or serpiginous ulcers which are asymmetrical in distribution	Diffuse, small, superficial with erythema, edema, loss of vascular pattern and friability
Discontinuous (skip) lesions	Yes	No
Bowel involvement	Transmural	Mucosal
Granulomas on histology	Yes	No

Except when clinical, laboratory and endoscopic findings are suggestive of typical UC, an evaluation of the small bowel by imaging is mandatory at diagnosis. Magnetic resonance enterography (MRE) is the recommended imaging modality and is preferred over CT largely due to high diagnostic accuracy and lack of radiation exposure. It can help to define disease activity, distinguish between inflammatory, stricturing and penetrating disease and can demonstrate both mural and extramural complications. However, CT enterography may be used to delineate small bowel disease (**Fig. 6**) in places where MR facilities/expertise is not available.

To assess the severity of UC or CD, various scoring systems have been devised which take into consideration clinical (stool frequency, nocturnal stools, general activity, abdominal pain and presence of blood in stools) and laboratory (hemoglobin,

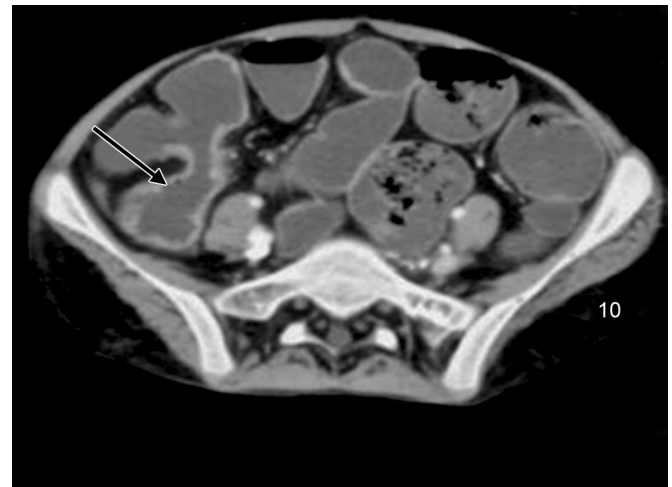


Figure 6 CT enterography showing thickening of ileum in a patient with Crohn's disease

albumin, ESR) parameters. The pediatric Crohn's disease activity index (PCDAI) is used for CD, while the pediatric ulcerative colitis activity index (PUCAI) is used for UC. They are useful for assessing response to therapy and comparing outcomes across studies.

DIFFERENTIAL DIAGNOSIS

Inflammatory bowel disease has to be differentiated from other causes of colitis like infective colitis, allergic colitis, pseudomembranous colitis, immunodeficiency and TB. The important points that help in differentiating between these conditions and IBD are as follows:

- *Infective colitis, i.e., dysentery*: The most common cause of colitis in children; seen at all ages; acute onset often with fever and occasionally with vomiting; short duration of illness of 5–7 days, rarely last for more than 2 weeks and good response to treatment with antibiotics.
- *Cow's milk protein allergy*: Onset less than 3 years of age; temporal association with introduction of bovine milk; features of eczema, wheezing; family history of atopy; definite response to milk withdrawal and reappearance with a challenge;

peripheral eosinophilia; and aphthous ulcers in rectum on proctosigmoidoscopy.

- **Pseudomembranous [*Clostridium difficile* (*C. difficile*)] colitis:** Seen at all ages; history of antibiotic intake; *C. difficile* toxin assay positive in stool; presence of pseudomembranes (yellowish gray plaques of 2–5 mm or larger) on colonoscopy are pathognomonic of *C. difficile* colitis. *C. difficile* colitis may occur in patients with IBD and should always be excluded in patients presenting with severe acute colitis.
- **Immunodeficiency:** Presents at an early age usually in infants or young children; family history of similar illness; history of infection at other sites, e.g., multiple episodes of respiratory or skin infections and liver abscesses. Chronic granulomatous disease may present with enterocolitis and perianal disease just like CD. Acquired immunodeficiency syndrome (AIDS) may present with colitis secondary to opportunistic infections like cytomegalovirus (CMV) colitis. Immunodeficiency work-up is required in few cases with immunoglobulin profile, test of phagocytic function and retrovirus serology.
- **Intestinal tuberculosis:** Intestinal TB often masquerades as CD in its clinical features. Colonic ulcers are circular in TB and longitudinal (along the long axis of colon) in CD. Cecum and ileocecal valve involvement is more common in TB. Ascites and necrotic abdominal lymph nodes are seen in TB. Granulomas are larger and show caseation in TB. Presence of acid fast bacilli on histology confirms the diagnosis of TB. It is essential to diagnose CD or TB correctly as the treatment for these two conditions is different and immunosuppression in a patient with intestinal TB may lead to disease flare and poor outcome.

TREATMENT

Medical Management

Inflammatory bowel disease is a disease of remissions and relapses. The goal of medical therapy is to induce and maintain remission (**Table 2**) and prevent disease complications with the

Table 2 Induction and maintenance therapy in patients with Crohn's disease and ulcerative colitis

Therapy	Crohn's disease	Ulcerative colitis
Induction	<p>Mild or moderate disease</p> <ul style="list-style-type: none"> • Oral prednisolone or • Exclusive enteral nutrition <p>Severe disease</p> <ul style="list-style-type: none"> • Intravenous steroids or • Infliximab <p>5-ASA may be effective in mild disease</p> <p>Antibiotics [metronidazole (7.5 mg/kg/dose TDS)/ciprofloxacin (5 mg/kg/dose BD)] in perianal disease</p>	<p>Mild disease</p> <ul style="list-style-type: none"> • Oral 5-ASA ± Topical mesalamine <p>Moderate or severe</p> <ul style="list-style-type: none"> • Oral prednisolone <p>Acute severe colitis</p> <ul style="list-style-type: none"> • Intravenous steroids (1st line) • Infliximab or IV cyclosporine (2nd line) • Surgery (failure of medical therapy)
Maintenance	<p>Immunomodulators (Azathioprine/6-MP/or methotrexate) or</p> <p>Infliximab and other biologicals (severe disease)</p>	<p>5-ASA preparation or</p> <p>Azathioprine/6-MP (in frequent relapsers)</p>

Abbreviations: ASA, aminosalicic acid; IV, intravenous; MP, mercaptopurine.

minimum possible medications. Apart from the control of disease activity, maintenance of nutrition and bone health and prevention of infections by appropriate immunization is important. The main drugs used for treatment of children with IBD are as follows (**Table 3**).

Steroids They have a central role as an induction agent in CD and moderate to severe UC. Prednisolone, in a dose of 2 mg/kg/day (maximum 40 mg/day) for 2–4 weeks followed by gradual tapering over 6–8 weeks achieves clinical remission in majority of cases. They are not used as maintenance therapy. The principles of steroid use in IBD are as follows—use an effective dose, do not overdose, do not treat for excessively short periods, do not treat for excessively long periods and anticipate side effects. Adequate dietary supplementation with calcium and vitamin D is essential to prevent bone disease.

5-aminosalicylic acid (ASA) agents They act by modifying neutrophil mediated tissue damage, by inhibition of leukotriene biosynthesis via the lipoxigenase pathway and scavenging of reactive oxygen species. Oral 5-ASA compound are recommended as first-line induction therapy for mild to moderately active UC and also for maintenance therapy in patients with UC. In CD its use is limited as an adjunctive role in isolated colonic CD as an induction agent. Combining oral 5-ASA with topical 5-ASA (enema, suppository) is more effective than oral alone. Sulfasalazine consists of 5-ASA in aza bond linkage with sulfapyridine. The sulfa moiety here acts as

Table 3 Dosage and side effects of medication used for treatment of inflammatory bowel disease (IBD)

Medication and dose	Side effects	Monitor
<p>Steroids</p> <ul style="list-style-type: none"> • Oral prednisolone (1–2 mg/kg/day) • IV methyl prednisolone (2 mg/kg/day) 	<p>Common: Acne, moon facies, hirsutism, cutaneous striae</p> <p>Uncommon: Steroid psychosis, hypertension proximal myopathy, growth impairment, osteoporosis, cataract and raised intraocular pressure</p>	<ul style="list-style-type: none"> • Blood pressure • Ophthalmic evaluation
<p>Aminosalicylate</p> <ul style="list-style-type: none"> • Mesalamine (50–100 mg/kg/day) • Sulfasalazine (40–60 mg/kg/day) 	<ul style="list-style-type: none"> • Vomiting, headache, diarrhea • Stevens-Johnson syndrome, pulmonary fibrosis, hepatotoxicity, agranulocytosis and mild hemolysis 	<ul style="list-style-type: none"> • CBC • LFT • Creatinine
<p>Immune modulator</p> <ul style="list-style-type: none"> • Azathioprine (2–2.5 mg/kg/day PO) • 6-mercaptopurine (1–1.25 mg/kg/day PO) • Methotrexate (15 mg/m²/week—PO/SC) 	<ul style="list-style-type: none"> • Bone marrow suppression, pancreatitis and increased risk of infections • Hepatotoxicity 	<ul style="list-style-type: none"> • CBC • Amylase • LFT
<p>Biologicals</p> <p>IV infliximab (5 mg/kg/dose at 0, 2 and 6 weeks and 4–8 weeks thereafter for maintenance)</p>	<p>Infusion reactions, flare of infections (TB, hepatitis B), demyelinating diseases, psoriatic rash</p>	<p>Screen for sepsis/TB before therapy</p>

Abbreviations: CBC, complete blood count; LFT, liver function tests; TB, tuberculosis; IV, intravenous; PO, per oral; SC, subcutaneous.

a carrier delivering the pharmacological active ASA moiety to the colon.

Immunomodulators These include drugs like azathioprine, 6-mercaptopurine (6-MP) and methotrexate. Thiopurines (AZA, 6-MP) take about 3 months to be fully effective and therefore cannot be used to induce remission. They have a role in steroid refractory [defined as active disease despite an adequate dose (1–2 mg/kg or minimum 20 mg/day) and duration (2 weeks) of steroids] and steroid dependent [relapse when steroids are tapered to 10 mg/day/frequently relapsing (≥ 2 relapses/year)] cases as a steroid sparing agent. Some centers add azathioprine from the beginning in severe cases to prevent subsequent relapses and repeated use of steroid.

Biologicals These include various antitumor necrosis factor alpha (anti-TNF- α) agents like infliximab, adalimumab and anti- α -integrin agents like natalizumab. These are potent and expensive medications indicated for induction and maintenance of severe luminal or fistulizing CD or induction of severe active UC refractory to steroid treatment. Infliximab is administered as an infusion at a dose of 5 mg/kg/dose at weeks 0, 2 and 6 and thereafter at 8-week intervals for maintenance.

Exclusive enteral nutrition (EEN) Exclusive enteral nutrition, in which a specific liquid formula (elemental, semi-elemental, or polymeric) is given without any other food item for 6–8 weeks, has been used for inducing remission in pediatric CD. Postulated mechanisms of action have included elimination of dietary antigens, overall nutritional repletion, correction of intestinal permeability, diminution of intestinal synthesis of inflammatory mediators via reduction in dietary fat, and provision of important micronutrients. EEN is as effective as steroids in inducing remission in newly diagnosed and active CD. EEN promotes mucosal healing and has beneficial effect on linear growth. The disadvantages of EEN include the high cost of the formula and the fact that the child cannot eat anything else for 6–8 weeks.

Surgery

Ulcerative colitis Surgery with restorative proctocolectomy (ileoanal pouch anastomosis) is curative and the surgical procedure of choice. The indications for surgery in UC patients are: acute severe colitis refractory to medical therapy; toxic megacolon; colonic perforation; uncontrolled GI hemorrhage; chronic ongoing disease with steroid dependence and colonic dysplasia or carcinoma.

Crohn's disease In CD surgery is not curative and management is directed at minimizing the impact of disease. At least 30% of patients require surgery in the first 10 years of disease and approximately 70–80% will have surgery in their lifetime. Surgery is indicated for bowel obstruction, drainage of abscesses, nonhealing fistulae, perforation or GI bleeding. Surgery should be considered for those in whom medical treatment has failed. In view of the chronic disease, attempts should be made to minimize intestinal resection and prevent short gut.

A close collaboration between gastroenterologist and surgeon experienced in pediatric IBD is essential for a good outcome.

Supportive Therapy

Nutritional therapy Recognition and correction of malnutrition by provision of adequate calories and proteins is important. The details of growth, pubertal status, disease mapping (site, extent and resections) and drugs administered should be noted. Anemia is

seen commonly and is multifactorial due to iron deficiency (blood loss), vitamin B₁₂ deficiency (terminal ileal disease/resection), folate deficiency (use of methotrexate, sulfasalazine) and chronic disease. Recognition of the type of anemia and appropriate supplementation of iron, B₁₂ or folate should be done. *High-risk* children with IBD, i.e., those with growth failure, pubertal delay, vertebral fractures and prolonged steroid therapy should have a dual X-ray absorptiometry (DXA) scan for assessment of bone mineral density. Appropriate supplementation of vitamin D and calcium is essential.

Immunization Inflammatory bowel disease patients are treated with immunosuppressant medications which increase the risk of developing infections, several of which can be prevented by appropriate vaccination. A detailed history of prior immunization and illnesses suffered should be taken in all patients. Ideally, an effort should be made to immunize pediatric patients with IBD with age appropriate live viral vaccines [e.g., *varicella* and measles, mumps and rubella (MMR)] before starting immunosuppressive therapy. Treatment with high-dose systemic corticosteroids (≥ 2 mg/kg/day of prednisone or ≥ 20 mg/day of prednisone or its equivalent for ≥ 14 days), cyclosporine or tacrolimus, thiopurines, methotrexate or biological is defined as immunosuppressive therapy. It is recommended that patients wait at least 1 month after discontinuing corticosteroids before immunization with *varicella* vaccine. However, inactivated vaccines can be safely given even along with immunosuppressant therapy.

COMPLICATIONS AND PROGNOSIS

The disease course is characterized by remissions and exacerbations. The complications depend upon the disease extent and severity of IBD. Patients with severe disease are more likely to require prolonged immunosuppressive therapy and surgical interventions, which increases the risk of short bowel and adhesive intestinal obstruction. The risk of colon cancer is increased in patients with UC and CD (with colonic involvement) and they should undergo screening colonoscopy with surveillance biopsies every 1–2 years, beginning approximately 7–10 years after their initial diagnosis. Patients who require therapy with immunomodulators and biologicals also have an increased risk of non-Hodgkin lymphoma. Children with IBD are at increased risk of having depression, social isolation, poor self-esteem and poor scholastic achievement due to chronic illness and school absences. Appropriate screening and attention to these psychosocial issues can improve the clinical outcome and health-related quality of life of these children.

PREVENTION

Efforts towards prevention of IBD by manipulation of gut microflora, exposure to helminths in childhood and dietary alterations (e.g., intake of polyunsaturated fatty acids, curcumin) are still in experimental stages. Prevention in IBD is therefore largely limited to preventing side effects related to disease management. Children with IBD, specifically CD, are at risk of exposure to ionizing radiation secondary to repeated medical imaging. Radiation has increased risk of cancer in children and therefore it is important to limit radiation exposure by using appropriate imaging modalities like ultrasonography, MRI and endoscopy. The combination of immunosuppressive medications places children with IBD at increased risk of opportunistic infections. Population studies suggest that there is an increased risk of thromboembolism in children with IBD (UC more than CD)

compared to controls. Good control of disease activity and mucosal healing are paramount to achieve adequate growth, timely puberty and bone health. Meta-analysis of patients requiring surgery has shown that ileal pouch-anal anastomosis (IPAA) increases the risk of infertility compared to medical management alone and this should always be considered and discussed with the family.

MORE ON THIS TOPIC

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IN A NUTSHELL

1. Inflammatory bowel disease includes Crohn's disease (CD), ulcerative colitis (UC) and inflammatory bowel disease unclassified (IBDU).
2. Nearly, 20–25% of all IBD has onset in childhood (< 18 years) with most children being diagnosed at 10–14 years of age.
3. The etiopathogenesis of IBD involves interplay between genetic factors, environmental triggers and gut microflora which initiates an abnormal mucosal immune response and leads to intestinal inflammation.
4. Crohn's disease can involve any part of the GI tract from mouth to rectum whereas UC is limited to the colon. Correct diagnosis of IBD and its subtype, i.e., UC or CD is essential as the management and outcome differs.
5. Loose stools with blood and mucus, i.e., features of colitis are the most common presentation. In addition, CD may present with abdominal pain, growth failure or small bowel type of diarrhea.
6. Extraintestinal manifestations (arthralgia, arthritis, EN, pyoderma gangrenosum, sclerosing cholangitis, uveitis, etc.) are seen in 6–28% children with IBD.
7. Diagnosis of IBD should be based on a combination of history, physical examination, laboratory evaluation, EGD with biopsy, ileo-colonoscopy with biopsy and small bowel imaging.
8. Treatment comprises of an induction phase (5-ASA, steroids, enteral nutrition, biological), followed by a maintenance phase (5-ASA, immunomodulators and biological).
9. Surgery is reserved for patients refractory to medical therapy or those with complications like toxic megacolon, perforation or hemorrhage.
10. Achieving optimal growth, timely puberty and prevention of bone disease is a very important aspect of management of children with IBD.

Chapter 35.18

Celiac Disease

Lalit Bharadia

Celiac disease (CD) is an immune-mediated systemic disorder elicited by gluten and related prolamines in genetically susceptible individuals. It is characterized by the presence of a variable combination of gluten-dependent clinical manifestations, CD-specific antibodies, human leukocyte antigen (*HLA*)-*DQ2* or *HLA-DQ8* haplotypes, and enteropathy. CD has a prevalence of 0.8–2.67% in the Western world. In one of the large population studies in Northern India, the prevalence was 15.44% by serology and 1.04% by histology. In India the disease is not only underdiagnosed because of varied and nonspecific clinical symptoms, but also delayed due to lack of awareness.

The prevalence of CD, as well as other autoimmune disorders like type 1 diabetes, has greatly increased in recent years, for reasons that are currently unclear but are likely related to environmental changes. Samuel Gee, in 1888, published the first complete modern description of the clinical picture of CD and stressed the importance of diet in its control. By 1952, Willem Dicke recognized that the disease is caused by the ingestion of wheat proteins, and not carbohydrates.

PATHOGENESIS

Celiac disease is a disease of genes and grains. *HLA* class II genes play an important role in the disease pathogenesis. Most patients with CD carry a variant of *HLA-DQ2* (DQ2.5; DQA1*05/DQB1*02), whereas the remaining patients carry *HLA-DQ8* (DQA1*03/DQB1*0302). The *HLA* genes present gluten peptide to T-cells which function as central effector cells of inflammation by releasing different cytokines, notably, interferon (IFN) γ , a key marker of the inflammatory Th1 response. The release of these cytokines precipitates a cascade of immune, mesenchymal, and epithelial cell activation in the small intestine, resulting in the hallmark lesions of crypt hyperplasia, villus atrophy and increased intraepithelial lymphocytes (IELs) (**Fig. 1**).

In addition to genetics, grains play an important role in the pathogenesis of CD. Gluten is the most significant identified factor. Dietary gluten contains several distinct T-cell epitopes rich in proline and glutamine residues. The high-proline content of dietary gluten leads to peptides that are not easily degraded by gastrointestinal (GI) proteases, leading to an elevated concentration of potentially immunogenic epitopes in the small intestine. IgA-transglutaminase 2 (TG2), a ubiquitous intracellular and facultative extracellular enzyme that can associate with the extracellular

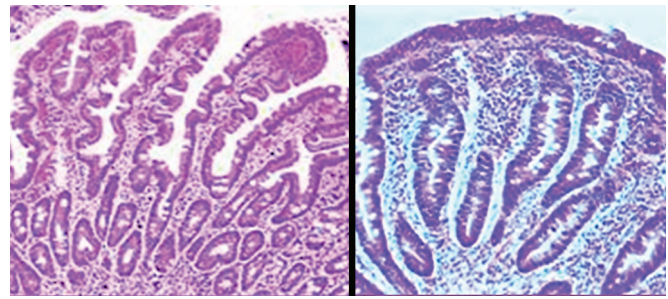


Figure 1 Normal histology (left) and total villus atrophy (right) in celiac disease

matrix, plays a central role in CD. TG2 targets certain glutamine residues found in dietary gluten and deamidates them to negatively charged glutamic acid residues. The negatively charged gluten peptides are able to bind with greater affinity to *HLA-DQ2* or *HLA-DQ8*, leading to enhanced gluten-specific CD41 Th1 cell activation.

CLINICAL FEATURES

There are four different clinical presentations of CD as shown in **Table 1**. On the basis of clinical presentation, symptomatic CD is broadly divided into typical and atypical CD. Because of its varied manifestations, atypical CD runs the risk of delayed diagnosis. With the use of serologic markers, the spectrum of CD has further widened to include potential and latent CD. **Box 1** shows the common extraintestinal manifestations of CD. In a recent study from North America, up to 55% children with CD did not have chronic diarrhea. A similar Indian study reported a figure of 36%.

Recent Oslo definitions have discouraged use of the terms typical, atypical, silent and latent celiac and suggested the use of classical, nonclassical, asymptomatic and latent CD respectively. Those asymptomatic patients who improve after gluten-free diet (GLD) in any manner (e.g., improvement in fatigue) are labeled as subclinical CD. Groups that are at risk of having silent CD are listed in **Table 2**. National Institute for Health and Clinical Excellence (NICE) Clinical Guidelines 2009 on CD recommend offering serological test to those mentioned in **Table 3** and considering offering the same to those in **Table 4**.

DIAGNOSIS OF CELIAC DISEASE

European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) Guidelines of 2012 for are the current standard for management of CD. This guideline describes two algorithms—one for symptomatic and another for high-risk asymptomatic groups.

Table 1 Presentations of celiac disease

Type	Presentation
Typical	<ul style="list-style-type: none"> • Predominant gastrointestinal signs/symptoms • Vomiting • Anorexia • Constipation • Diarrhea • Failure to thrive • Recurrent abdominal pain
Atypical or extraintestinal	Gastrointestinal signs/symptoms are minimal or absent. Most common extraintestinal manifestations described in Box 1 .
Silent	No signs/symptoms. Gluten dependent duodenal mucosa are typical of celiac disease
Latent	Signs, symptoms may or may not be present. Duodenal mucosa normal. Gluten dependent changes with or without symptoms appear later in time

BOX 1 Extraintestinal manifestation of celiac disease

- Dermatitis herpetiformis
- Permanent enamel hypoplasia
- Iron-deficient anemia resistant to oral iron supplements
- Short stature, delayed puberty
- Chronic hepatitis
- Arthritis
- Osteopenia/osteoporosis
- Epilepsy with occipital calcifications
- Primary ataxia, white matter-focal lesions
- Psychiatric disorders.

Table 2 Groups that are at risk of having silent celiac disease

Condition	Approximate prevalence of celiac disease (%)
Type 1 diabetes mellitus	8–10
Thyroiditis	3–5
Sjögren syndrome and other connective tissue disorder	3–4
Down syndrome	10–12
William syndrome	5
Turner syndrome	5
First degree relative of celiac patient	8–10

Table 3 Situations which warrant serologic testing for celiac disease (CD)

Signs and symptoms	Conditions
Chronic or intermittent diarrhea	Autoimmune thyroid disease
Failure to thrive	Dermatitis herpetiformis
Persistent or unexplained GI symptoms including nausea and vomiting	Irritable Bowel syndrome
Prolonged fatigue	Type 1 diabetes
Recurrent abdominal pain, cramping or abdominal distension	First degree relative with celiac disease
Sudden or unexpected weight loss	
Unexplained iron deficiency anemia or unspecified anemia	

Table 4 Consider offering serological testing to children and adults with any of the following

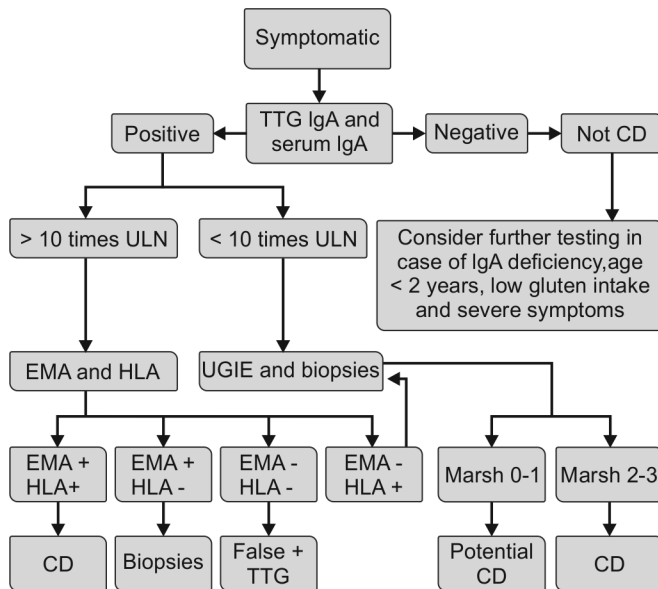
Addison disease	Microscopic colitis
Amenorrhea	Persistent or unexplained constipation
Aphthous stomatitis (mouth ulcers)	Persistently raised liver enzymes with no cause
Autoimmune liver disease	Polyneuropathy
Autoimmune myocarditis	Recurrent miscarriages
Chronic thrombocytopenic purpura	Reduced bone mineral density
Dental enamel defects	Sarcoidosis
Depression or bipolar disorder	Sjögren syndrome
Down syndrome	Turner syndrome
Epilepsy	Unexplained alopecia
Low trauma fracture	Unexplained subfertility
Lymphoma	
Metabolic bone disease	

The *symptomatic group* should first be offered serology (**Flow chart 1**), as against the previous guidelines which insisted on duodenal biopsies for the diagnosis of CD. If serology is more than 10 times the upper limit of normal, duodenal biopsies may be omitted, provided an additional serologic test and HLA are both positive. In all other children, a duodenal biopsy must be done to confirm CD. Symptomatic children who are negative for serology may require, further testing if they are less than 2 years of age, have immunoglobulin A (IgA) deficiency, have severe symptoms or have been on a low gluten diet at presentation.

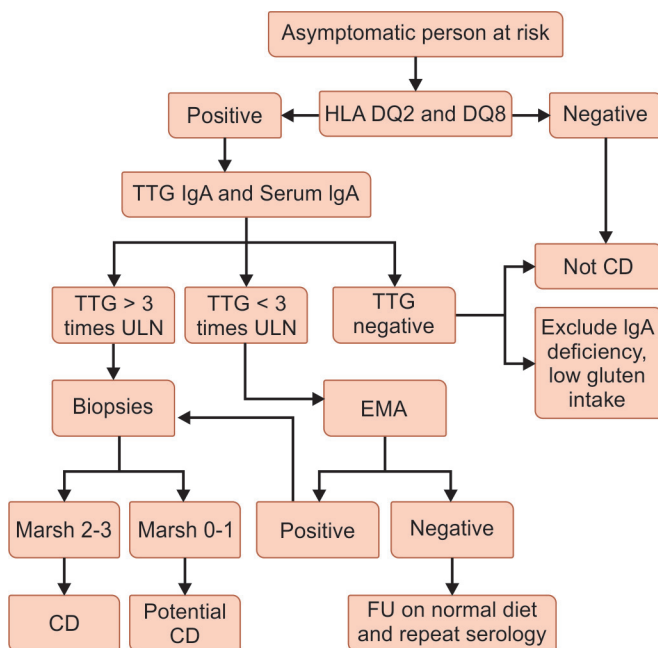
The *asymptomatic group* who are investigated because of their increased risk for the disease should first be offered HLA test (**Flow chart 2**). Those positive for *HLA-DQ2* or *-DQ8* should be tested for serology and offered duodenal biopsy if serology is more than three times upper limit normal. If serology is less than three times upper limit of normal, a repeat serology should be done after 3–6 months.

Which Serological Test

- Immunoglobulin A tissue transglutaminase (tTGA) is the first screening test.
- Immunoglobulin A endomysial antibodies (EMA) testing if the result of the tTGA test is equivocal.
- Check for IgA deficiency if the serology is negative.
- Immunoglobulin G tTGA and/or IgG EMA serological tests are for people with confirmed IgA deficiency.
- In children less than 2 years of age, deamidated gliadin peptide (DGP) IgG is better than other tests.

Flow chart 1 Guideline for diagnosis of symptomatic patient

Abbreviations: TTG, tissue transglutaminase; CD, celiac disease; EMA, endomysial antibodies; F/u, follow-up; GFD, gluten-free diet; HLA, human leukocyte antigen; IgA, immunoglobulin A; IgG, immunoglobulin G; UGIE, upper gastrointestinal endoscopy; ULN, upper limit of normal.

Flow chart 2 Diagnosis of celiac disease in asymptomatic patient

Abbreviations: TTG, tissue transglutaminase; CD, celiac disease; EMA, endomysial antibodies; F/u, follow-up; GFD, gluten-free diet; HLA, human leukocyte antigen; IgA, immunoglobulin A; IgG, immunoglobulin G; UGIE, upper gastrointestinal endoscopy; ULN, upper limit of normal.

Upper GI Endoscopy

While performing the upper GI endoscopy, biopsies should be taken preferably from the duodenal bulb (at least one biopsy) and from the second or third portion of duodenum (at least four biopsies). The various endoscopic duodenal appearances which suggest CD include mosaic pattern (in 100%), scalloped folds of

duodenum (70%) (**Figs 2A and B**), visible vasculature (15%) and reduced folds of duodenum (6%). The pathology report should include a description of the orientation, the presence or not of normal villi or degree of atrophy and crypt elongation, the villus-crypt ratio, the number of IELs, and grading according to the Marsh-Oberhuber classification.

The enteropathy in CD is of variable severity and may be patchy, with changes present only in the duodenal bulb in some patients. The histological appearance is not specific for CD and may be found in other enteropathies as well. The characteristic histological changes in CD are increased IELs (> 25/100 enterocytes), increased crypt length, partial to total villus atrophy, decreased villus crypt ratio and infiltration of plasma cells and lymphocytes in the lamina propria. The histological changes are graded according to modified Marsh criteria as follows:

- Grade 0—Normal
- Grade 1—Infiltrative (increased IEL)
- Grade 2—Hyperplastic (grade 1 + hyperplastic crypt)
- Grade 3a—Partial villus atrophy
 - 3b—Subtotal villus atrophy
 - 3c—Total villus atrophy (23)
- Grade 4—Hypoplastic (total villus atrophy + hypoplastic crypts).

Marsh 3 and 4 are characteristic of CD. Marsh 2 is compatible with CD but needs serological positivity for definite diagnosis while Marsh 1 is not specific for CD in children.

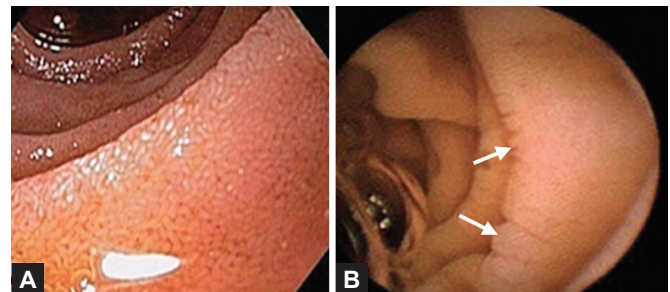
Human Leukocyte Antigen Testing

The principal determinants of genetic susceptibility for CD are the major histocompatibility class II *HLA* class II *DQA* and *DQB* genes coded by the major histocompatibility region in the short arm of chromosome 6. More than 95% of patients with CD share the *HLA-DQ2* heterodimer and most of the remaining have the *HLA-DQ8* heterodimer. CD is a multigenetic disorder, which means that the expression of these *HLA-DQ2* or *HLA-DQ8* molecules is necessary but not sufficient to cause disease. Approximately 30–40% of the white population holds the *HLA-DQ2* haplotype, while only 1% of them develop CD.

Human leukocyte antigen testing should be performed in patients with an uncertain diagnosis of CD, for example, in patients with negative CD-specific antibodies and mild infiltrative changes in proximal small intestinal biopsy specimens. HLA testing may be offered to asymptomatic individuals with CD-associated conditions (group 2) to select them for further CD-specific antibody testing.

TREATMENT

All children with proven CD must be started on GFD. An unequivocal response to GFD within few weeks to months confirms the diagnosis of CD. A strict GFD for life is the cornerstone of treatment. Patients need to be counseled in local language on the specific cereals to be avoided. In India, wheat and barley (*Jaun*)



Figures 2A and B (A) Normal endoscopic appearance of duodenum; (B) Characteristic scalloped folds of duodenum in celiac disease

are the most commonly used grains which contain gluten. *Rye* is another gluten containing cereal used to make breads in some parts of Europe, but is not available in India. In India, mustard (*Rai*, *Sarson*) is often wrongly excluded from diet, since it sounds similar to *Rye*. Sorghum (*Jowar*) is also wrongly excluded due to confusion with barley (*Jaun*). Pure oats (*Jae*) does not contain gluten, but often gets contaminated with gluten during milling and harvesting. If purity is ensured, oats can be allowed. Patients and families need to be educated about sources of accidental contamination of gluten (e.g., common grinding machine or common cooking place for gluten and gluten-free food) and also about reading the ingredients of any ready to eat food. While no mention of *wheat* or *barley* in the contents is reassuring, a reliable label of *gluten free* is ideal. Supportive nutritional care to prevent vitamin, iron and calcium deficiency is required.

Although a *zero tolerance* policy is recommended, it is known that sensitivity to ingested gluten varies greatly amongst patients. A recent meta-analysis estimated, that gluten in amounts less than 10 mg/day may be safe to consume, while more than 100 mg/day are likely to result in the majority of patients exhibiting some signs of immune reactivation and/or symptoms. A typical western diet contains an average of 156 g of wheat (i.e., 40 g of gluten) a day. On a strict GFD, GI symptoms resolve within a few weeks, followed by normalization of biochemical parameters and finally increase in weight and height. Treatment with GFD also reverses the decrease in bone mineralization as well as risk for fractures. There is also marked improvement in their sense of physical and psychological well-being, as documented by a recent quality of life study.

REFRACTORY CELIAC DISEASE

Refractory celiac sprue is defined as symptomatic severe enteritis that does not respond to a strict GFD even after 6 months, without any other causes of enteropathy or overt intestinal lymphoma. It is rare in children and usually seen in elderly patients with poor nutritional status because of chronic malabsorption and protein losing enteropathy. Such patients require treatment with corticosteroids and immunosuppressants, like azathioprine or cyclosporin as well as total parenteral nutrition.

FOLLOW-UP AND MONITORING

If the diagnosis of CD is made according to the diagnostic criteria mentioned above, the family should receive professional dietary counseling for a GFD. They should be followed up regularly for growth monitoring as well as for re-emphasizing the need for lifelong GFD. The CD specific antibody titers fall to below normal within 12 months after starting therapy. If there is no clinical response to a GFD in symptomatic patients, a careful dietary re-assessment should be done to exclude lack of compliance. If none is found, further investigations are required to look for coexisting food intolerances.

Gluten challenge is considered necessary in situations where there is doubt about the initial diagnosis. Gluten challenge should be preceded by HLA typing and assessment of mucosal histology and should be performed under medical supervision. Gluten

challenge should be discouraged in children below 5 years of age and during the pubertal growth spurt, unless the child is *HLA-DQ2* and *HLA-DQ8* negative or has been placed on a GFD without proper testing. The daily gluten intake during gluten challenge should contain at least the normal amount of gluten intake for children (approximately 15 g/day). IgA anti-TG2 antibody (IgG in low levels of serum IgA) should be measured during the challenge period. A patient should be considered to have relapsed (and hence the diagnosis of CD confirmed) if CD-specific antibodies become positive and a clinical and/or histological relapse is observed. In the absence of positive antibodies or clinical symptoms, the challenge should be considered completed after 2 years. However, additional biopsies on a normal diet are recommended because delayed relapse may occur later in life.

PROGNOSIS

Gluten-free diet usually results in clinical, serologic, and histologic remission. In the long-term, it not only reduces the risk of malignancies, but also protects against developing autoimmune diseases such as IDDM, hematologic disorders, and inflammatory bowel disease. In western countries, adherence to a GFD in the general population is reported to be less than 50%, but may be as high as 81% in children. Studies from the developing world have reported a GFD adherence of 45–100%. Those who start a GFD below 10 years of age are 1.3–2 times more compliant. Maintaining a strict long-term GFD is a challenge, especially in children and adolescents. Noncompliance is due to several factors including ignorance about the diet, social/peer pressure, nonavailability of commercially available GFD, dislike of the taste of alternative food, increased outdoor activities, increased risk-taking behavior, and conflicts with parents. Adherence to a GFD is lower in asymptomatic patients who are diagnosed through a mass screening program, than in those referred because of clinical suspicion. In addition, more than 30% of those who think that they are adhering to a GFD are consuming gluten-contaminated food daily. The benefits of adherence to a GFD have been well documented in even in developing countries. Demir and colleagues reported improvement in growth rate in Turkish children with CD adhering to a GFD. Moreover, diabetic children with CD adhering to a GFD have fewer hypoglycemic episodes and better diabetic control. Zamani and colleagues found that Iranian patients with CD with IDA who are on a GFD had spontaneous recovery of their anemia even without iron supplementation.

Problems with therapy Currently, the only available therapy for CD is strict lifelong adherence to a GFD. Although the GFD is a safe and effective therapy, there are practical problems in enforcing it. Guidelines for permissible gluten content in gluten free products vary across the globe and monitoring is lacking in most developing countries. GFD is expensive, not readily available in many countries, and may be lower in its nutritional value, which can significantly impact patient adherence and quality of life. In addition there are issues related to social stigma in communities where awareness about the disease is poor. Alternatives to GFD is desirable and future possible therapies are shown in **Table 5**.

Table 5 Newer therapies for celiac disease

Target	Approach
Gluten modification	Modified grain, pretreated flour, oral glutenase
Intraluminal therapies	Gluten sequestering polymers, gluten neutralizing antibodies
Immune modification	Gluten vaccination
Modification of intestinal permeability	Zonulin receptor antagonist
Immune cell targeted therapies	Immunosuppressant

IN A NUTSHELL

1. Celiac disease (CD) is prevalent in 1% of general population in north India.
2. Due to its varied presentation, it runs the risk of remaining undiagnosed and delayed diagnosis in significant number.
3. Except in a minority of symptomatic children with two serologies and HLA DQ2/DQ8 positive, all other need duodenal biopsies for confirmation of CD.
4. Lifelong strict gluten free diet remains the only treatment for CD currently.

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Chapter 35.19

Abdominal Tuberculosis

Yogesh Waikar

Abdomen is a common site of extrapulmonary tuberculosis (TB) in children. It can involve the gastrointestinal (GI) tract, mesenteric lymph nodes or peritoneum. The diagnosis is difficult, since clinical features are varied as well as nonspecific. About 10% of all cases of abdominal TB occur under the age of 10 years.

PATHOGENESIS

The tubercle bacillus reaches the GI system by hematogenous spread from the primary lung focus, ingestion of bacilli from the sputum from an active pulmonary focus, direct spread from adjacent organs or through lymph channels from infected abdominal nodes. Ileocecal region is commonly involved. Mesenteric and peritoneal TB are seen in approximately one-third of patients. The initial infection is localized to the *Peyer's patches* leading to local ulcers followed by mesenteric lymphadenitis and peritonitis.

Intestinal TB is commonly classified as ulcerative, ulcerohyperplastic and hyperplastic forms. Liver and spleen also can get involved by the tubercle bacillus leading to formation of tuberculoma. Peritoneal TB can be wet type with ascites or loculated ascites or fibrotic/plastic type with abdominal masses and omental thickening.

Esophageal TB is rare. It occurs mainly by extension of disease from adjacent intrathoracic lymph nodes. Duodenal TB is also rare, presenting as stricture. Abdominal TB can also present as malabsorption. Involvement of colon, rectum and anal canal in TB is rare.

CLINICAL FEATURES

Childhood abdominal TB is commonly seen in age group 7–15 years old. Fever, abdominal pain and/or discomfort and weight loss are common presenting symptoms. One of the most common differential diagnoses is Crohn's disease. The features of hematochezia, intestinal obstruction, fistula, oral ulcers, longitudinal ulcers, cobblestone appearance and pseudopolyps are more common in Crohn's disease than in intestinal TB. Hepatic TB presents with hepatomegaly. Tuberculoma and tuberculous liver abscesses are uncommon manifestations of hepatic TB. In miliary TB tubercles are seen near the hepatic veins. In localized forms of hepatic TB the portal vein appears to be the route of spread. TB can also involve pancreas and can present as acute or chronic pancreatitis.

APPROACH TO DIAGNOSIS

The following points are important in history: contact with an open case of TB; past treatment for pulmonary or extrapulmonary TB and features suggestive of an immunocompromised state. The following should be looked for on examination: peripheral stigmata of TB like lupus vulgaris, TB verrucosa cutis, cold abscess in neck, multiple ear drum perforations, scrofuloderma, lymphadenopathy, phlyctenular conjunctivitis, or spinal swelling. Associated involvement of other organs leading to respective manifestations should be screened, e.g., soft neurological signs of neurotuberculoma. Also obtain detailed anthropometry to determine the nutritional status. Examination of the abdomen should focus on the right iliac fossa. Subtle

signs of subacute intestinal obstruction should not be missed. Peritoneal TB commonly present as ascites which should be carefully looked for.

DIAGNOSIS

Imaging studies Chest X-ray needs to be done to rule out associated pulmonary TB, which may be seen in about 25% of cases. X-ray of the abdomen may show evidence of intestinal obstruction or surgical complications of the disease. Small bowel contrast meal follow through imaging may reveal involvement of terminal ileum and ileocecal junction. The most common abnormality is short-segment strictures with symmetrical concentric mural thickening and homogeneous mural enhancement. Lymphadenopathy, ascites, enteroliths, peritoneal thickening, and enhancement can also be made out. *Barium enema* may reveal the following findings:

- *Fleischner or inverted umbrella sign* suggestive of early involvement of ileocecal valve.
- *Conical cecum*: Cecum pulled out of iliac fossa due to contraction or fibrosis of mesocolon.
- *Purse string stenosis*: Localized stenosis opposite the ileocecal valve with a rounded off smooth cecum and a dilated terminal ileum.
- *Stierlin's sign*: Narrowing of the terminal ileum with rapid emptying into a shortened, rigid or obliterated cecum.
- *String sign*: Persistent narrow stream of barium suggest stenosis.

Cross-sectional imaging is useful in detecting abdominal lymph nodes. Mesenteric and periportal lymph nodes are involved more often in patients with abdominal tuberculosis, while iliac and inguinal lymph nodes are more with lymphoma. While peripheral enhancement is seen more often in tuberculous lymphadenopathy, homogeneous enhancement suggests lymphoma. Ultrasonography of abdomen may reveal ascites, loculated ascites, interloop ascites, mesenteric lymph nodes, bowel thickening, or pseudokidney sign (pulled up cecum).

Endoscopy On colonoscopy, mucosal nodules of variable sizes and ulcers in a discrete segment of colon, ulcer between nodules, and deformed ileocecal valve, are characteristic. Biopsies should be taken from the edge of the ulcers. The characteristic caseous granulomas are seen only in about one-third of cases. While acid fast bacilli (AFB) staining has a variable yield, cultures are rarely positive. Balloon-assisted and spiral enteroscopy with biopsy can be used for evaluating the small bowel. Upper GI endoscopy has limited role.

Others Ascitic fluid analysis shows a predominance of mononuclear cells. Ascitic fluid ADA (adenosine deaminase) greater than 39 IU/L can be used as adjunct test in diagnosis. Serum ascites albumin gradient (SAAG) is less than 1.1 g/dL in peritoneal TB. Ascitic fluid mycobacterial culture (after centrifugation) is positive in only 50% of cases. Laparoscopy with histology and culture of peritoneal biopsies has better sensitivity. Gastric lavage for AFB and positive *Mantoux test* are useful supportive investigations. Serological tests and nucleic acid amplification [e.g., polymerase chain reaction (PCR)] are not useful.

DIFFERENTIATING TB FROM CROHN'S DISEASE

Increased erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) may be seen in both TB and inflammatory bowel disease. Anti-*Saccharomyces cerevisiae* antibody (ASCA) is not useful in differentiating between Crohn's disease and TB. In one-third of cases tubercle bacilli can be cultured from mucosal

biopsies. Ascites, transverse ulcers, patulous ileocecal valve and granulomas are more common in intestinal TB than in Crohn's disease. Granulomas exceeding 300 μm in maximal diameter, more than five granulomas per section, and confluent granulomas are more frequently identified in intestinal TB than in Crohn's disease. Demonstration of caseating granuloma in the biopsy specimen is definitive. Granulomas of TB and Crohn's disease can be differentiated by CD73. Mesenchymal cells surface marker expression CD73 is expressed around the granulomas of TB alone and is absent in the Crohn's disease.

The sensitivity, specificity, positive predictive value and negative predictive value of T-SPOT-TB (interferon- γ release assay) are around 80–90%. Quantiferon-TB Gold test has many limitations and therefore not very useful. PCR using *Mycobacterium tuberculosis* complex-specific primers for IS6110 to differentiate TB and Crohn's disease is not sensitive enough. Correlation between PCR positivity and histological lesions such as caseation and granulomas is yet to be established. Immunohistochemical staining of biopsy specimens with anti-VP-M660 has high specificity but low sensitivity in differentiation.

MANAGEMENT

Abdominal TB comes in category of extrapulmonary TB and should be treated as $2\text{H}_3\text{R}_3\text{Z}_3\text{E}_3$ in intensive phase followed by $4\text{H}_3\text{R}_3$ in continuation phase as per the updated Revised National Tuberculosis Control Program with the Indian Academy of Pediatrics (RNTCP-IAP) guidelines. Previously incompletely treated abdominal TB may be considered to have in intensive phase regimen as $2\text{S}_3\text{H}_3\text{R}_3\text{Z}_3\text{E}_3 + 1\text{H}_3\text{R}_3\text{Z}_3\text{E}_3$. Follow-up therapy is recommended with $5\text{H}_3\text{R}_3\text{E}_3$. Abdominal TB in immunosuppressed patients and those with multidrug resistant TB are challenges which require specialist help. Strict drug compliance needs to be ensured to avoid emergence of multidrug resistant strains. Role of corticosteroids is controversial. Complications of abdominal TB depend on the site of involvement. They include ulcer, perforation, adhesion, obstruction, bleeding, fistulae formation and stenosis.

IN A NUTSHELL

1. The risk factors for abdominal TB are household contact with a newly diagnosed smear-positive case, age less than 5 years, human immunodeficiency virus (HIV) infection and severe malnutrition.
2. In wet type, peritoneal TB calculation of SAAG and ADA helps in diagnosing peritoneal TB.
3. The diagnosis of abdominal TB is based on clinical features, imaging of the abdomen and histology of the affected tissue. There is no role of serology to diagnose abdominal TB.
4. Abdominal TB in immunosuppressed patients or multidrug resistant TB should be managed with the help of pediatric infectious disease specialist and clinical microbiologist.

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Chapter 35.20

Ascites

Malathi Sathiyasekeran, R Ganesh

Ascites, defined as the pathologic accumulation of fluid (more than 25 mL in adults) within the peritoneal cavity. Ascites can occur at any age with varying etiological spectrum in the different groups.

INCIDENCE

In liver disease, the incidence of ascites depends on the underlying pathology. In cirrhosis, ascites is seen in 44%, in presinusoidal portal hypertension (PHT) in 10–12% and in more than 80% in postsinusoidal PHT. In acute liver failure and AVH it is seen in about 50% and 10% of patients, respectively.

ETIOPATHOGENESIS

The causes of ascites are shown in **Table 1**. Ascites can be broadly classified into cirrhotic and noncirrhotic ascites.

Noncirrhotic Ascites

Hepatic causes (a) *Acute viral hepatitis (AVH)*: Transient PHT due to sinusoidal collapse, spontaneous bacterial peritonitis (SBP) and hypoalbuminemia are possible explanations; (b) *Postsinusoidal PHT*: Ascites occurs when the hydrostatic and osmotic pressures within hepatic capillaries produce a shift of fluid from blood to the lymphatics at a rate which exceeds its drainage capacity; (c) *Presinusoidal PHT*: Ascites is uncommon in presinusoidal PHT but may occur following hemorrhage or surgery due to depressed hepatocellular function.

Pancreatic ascites Fluid initially accumulates due to leakage of pancreatic juice from a disrupted pancreatic duct or a pseudocyst. Further formation occurs secondary to *chemical burn* of the peritoneum.

Biliary ascites Bile may leak into the peritoneal cavity due to spontaneous or iatrogenic perforation of the bile duct.

Malignant ascites The malignant cells on the peritoneum produce fluid that is rich in protein which causes a rapid shift of fluid into the peritoneal cavity secondary to the osmotic drag.

Chylous ascites Rupture of obstructed or distorted abdominal lymphatics as occurs in congenital lymphangiectasia or other acquired conditions.

Tuberculous ascites Peritoneal tubercles secrete proteinaceous material causing an osmotic drag of fluid and present as either diffuse or loculated ascites.

Eosinophilic ascites In eosinophilic gastroenteritis (EGE), the eosinophils infiltrate the Peyer's patches and if the serosa is infiltrated it results in eosinophilic ascites.

Infections Transient ascites may occur in several febrile illnesses. Third spacing of fluid in dengue shock may cause ascites. In leptospirosis and typhoid fever the ascites is due to serositis.

Cirrhotic Ascites

Sinusoidal PHT is the initial mechanism that determines leakage of fluid into the peritoneal cavity. Sinusoidal PHT with increase in portal pressure is an essential component in the pathogenesis and ascites rarely develops unless the threshold pressure is more than 12 mm Hg. Hypoalbuminemia may predispose to fluid accumulation, but is not an essential component. Sodium and water retention causes increase in intravascular volume leading to ascites formation. The pathophysiology of cirrhotic ascites is shown in **Figure 1**.

A. Underfill theory: Portal hypertension results in decreased blood volume leading to decreased renal perfusion. This activates the plasma renin-aldosterone pathway and the sympathetic nervous system resulting in renal sodium and water retention and promotes ascites formation.

B. Overflow theory: An unknown hepatorenal reflex causes inappropriate sodium and water retention followed by increasing blood volume which together with PHT, leads to ascites.

C. Peripheral arterial vasodilation theory: The first step is vasodilation of the peripheral vessels leading to systemic hypotension and a decrease in cardiac output. This is followed by renal retention of sodium and water, plasma volume expansion and ascites. This theory has been modified and termed as *forward*

Table 1 Causes of ascites in children

Organ involved	Condition
Hepatic	<p><i>Chronic liver disease</i>: Portal hypertension(PHT)—Common</p> <p><i>Postsinusoidal PHT</i>: Hepatic venous outflow tract obstruction (HVOTO): Sinusoidal Obstruction syndrome, Budd-Chiari syndrome, IVC obstruction</p> <p><i>Sinusoidal PHT</i>: All causes of cirrhosis, e.g., HBV, HCV, Wilson's disease, tyrosinemia, autoimmune, biliary, malignancy</p> <p><i>Presinusoidal PHT</i>:</p> <ul style="list-style-type: none"> • <i>Intrahepatic presinusoidal</i>: Congenital hepatic fibrosis, noncirrhotic portal fibrosis (10%) • <i>Extrahepatic</i>: Extrahepatic portal venous obstruction (EHPVO): 5–10% <p><i>Acute liver disease</i>: Acute hepatitis, acute liver failure</p> <p><i>Traumatic</i>: Liver injury secondary to accidents, liver biopsy</p>
Biliary	Perforation of bile duct: Spontaneous, iatrogenic
Pancreas	Anterior disruption of pancreatic duct, rupture of pseudocyst
Luminal GI	Intestinal perforation, appendicitis, eosinophilic gastroenteritis (EGE)
Peritoneal	Tuberculosis
Renal	Nephrotic syndrome, peritoneal dialysis
Hematological	Hemolysis, tumors
Lymphatic	Primary intestinal lymphangiectasia, Hennekam syndrome
Cardiac	Complex cyanotic heart disease, CCF, arrhythmia
Vasculitis	Henoch-Schönlein purpura, connective tissue disorder, SLE
Infections	Dengue fever, salmonellosis, leptospirosis, scrub typhus
Malignancy	Wilms tumor, germ cell and ovarian tumors, metastasis
Pseudo ascites	Omental cyst, retroperitoneal lymphangioma

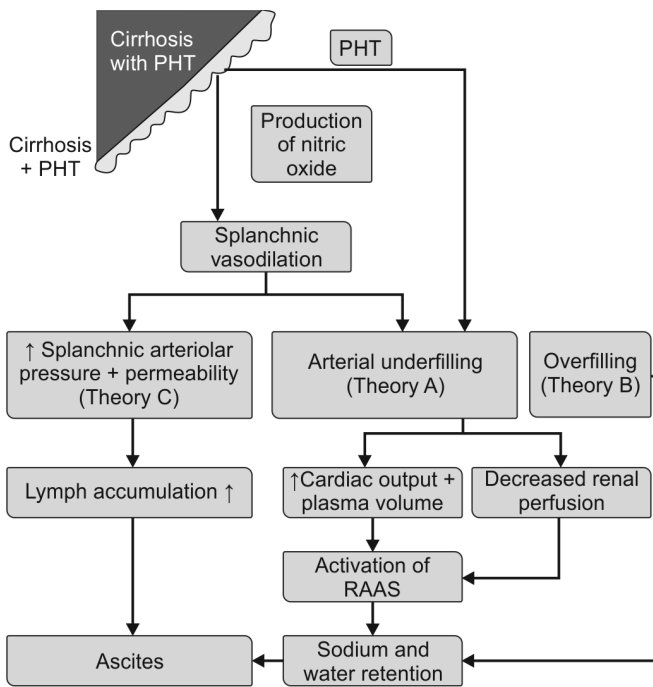


Figure 1 Pathophysiology of cirrhotic ascites

theory of ascites formation and combines arterial under-filling with a forward increase in splanchnic capillary pressure and filtration with increased lymph formation. In cirrhosis, several vasodilators such as the potent nitric oxide, calcitonin gene-related peptide, substance P, carbon monoxide and endogenous cannabinoids are produced which augment the ascites formation.

CLINICAL PRESENTATION

The child may be asymptomatic or have mild abdominal discomfort if the fluid is minimal. An increase in abdominal girth and weight gain may be early symptoms. Anorexia, nausea and growth failure are indicators of increasing ascites. When the ascites is massive and tense, the child presents with breathlessness and respiratory distress (Fig. 2). Pain is not present unless there is an infection such as spontaneous/secondary bacterial peritonitis or malignancy. Depending upon the etiology there may be additional features such as jaundice, gastrointestinal (GI) bleed and altered sensorium in cirrhotic ascites. Fever and contact with tuberculosis (TB) may be suggestive of TB ascites.

The physical findings are a protuberant abdomen, fullness of the flanks, formation of hernias (umbilical, inguinal or femoral) and smiling/inverted umbilicus. The presence of splenomegaly and prominent abdominal veins suggest sinusoidal PHT. Splenomegaly with minimal free fluid in the abdomen and absence of abdominal veins indicates presinusoidal PHT whereas massive ascites and back veins suggest postsinusoidal PHT. Tender hepatomegaly with distended jugular veins and elevated jugular venous pressure suggests cardiac ascites.

Complications

Mechanical Massive or tense ascites may cause respiratory distress, compression of great vessels, abdominal wall hernias (umbilical, inguinal or femoral), gastroesophageal reflux disease, delayed gastric emptying and obstructive sleep apnea syndrome. Pleural effusion or hepatic hydrothorax is a common finding in cirrhotic ascites.

Metabolic complications Dyselektrolytemia may occur secondary to diuretic use.



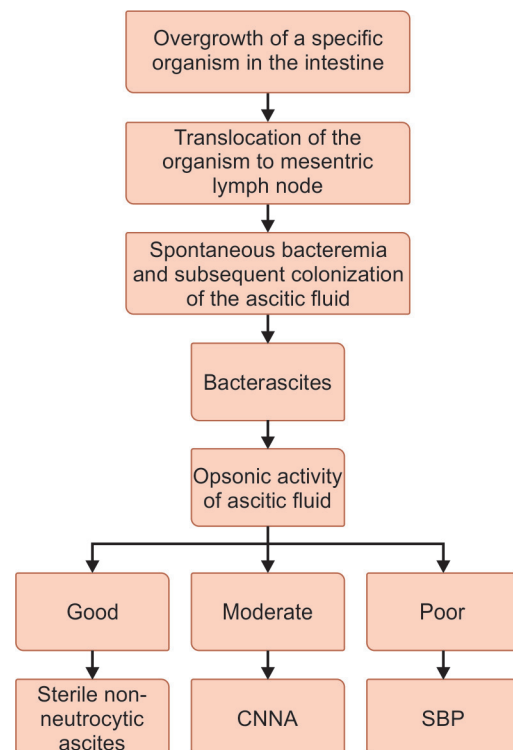
Figure 2 Child with tense ascites

Infection Spontaneous bacterial peritonitis (SBP) is an important complication of cirrhotic ascites seen in 10–30% of patients and is associated with a high mortality. SBP denotes infection of ascitic fluid without evidence of an abdominal source and is usually due to gram-negative bacilli (*E. coli*, *Klebsiella*) and gram-positive cocci (*Streptococcus pneumoniae*, enterococci). The pathogenesis of bacterial peritonitis is shown in Flow chart 1.

Hepatorenal syndrome (HRS) Hepatorenal syndrome is the functional renal failure that occurs in patients with decompensated liver disease, in the absence of an identifiable renal cause.

Differential diagnosis Pseudoascites caused by retroperitoneal lymphangioma, ovarian tumor, large mesenteric cyst can mimic true ascites.

Flow chart 1 Pathophysiology of spontaneous bacterial peritonitis



Abbreviations: CNNA, culture negative neutrocytic ascites; SBP, spontaneous bacterial peritonitis.

APPROACH TO A CHILD WITH ASCITES

Demonstration of Ascitic Fluid

Clinical Signs

Puddle or Lawson's sign This test detects a minimal amount (120 mL) of fluid and is beneficial in small children.

Shifting dullness This finding is based on the alteration of the percussion note in the flanks when the position is changed and the air filled loops are displaced by the fluid. In children at least greater than 500 mL is necessary for demonstration.

Fluid thrill Demonstration of a fluid wave indicates large amount greater than 1,000 mL of fluid in the peritoneal cavity. Ascites is graded according to the International club of ascites as Grade 0 if there is no demonstrable ascites, Grade 1 if mild ascites detected only by ultrasound, Grade 2 if moderate ascites without fluid thrill and Grade 3 if large/tense ascites with marked distension of abdomen and fluid thrill.

Imaging Studies

Plain abdomen skiagram reveals ground glass appearance, obliteration of the hepatic angle (Hellmer's sign), flank stripe sign and *mickey mouse sign*. On ultrasound (US) of the abdomen: Minimal peritoneal fluid (10–20 mL) has been detected in 7% of asymptomatic children. Limitations to ultrasound include obesity and complex, loculated ascites since fat and air are poor conductors of sonic waves. US also helps in the etiological diagnosis and guiding paracentesis. CT and MRI are as sensitive as US of abdomen in detecting fluid but cost is a limiting factor.

Diagnostic Abdominal Paracentesis

Diagnostic paracentesis is an essential part of the first evaluation. It is a simple, safe method for confirming diagnosis and identifying etiology. It is performed under local anesthesia following aseptic precautions and using the standard technique. Prophylactic platelet or fresh frozen plasma is not recommended prior to paracentesis.

Color The fluid may be watery or transparent in cirrhosis with hypoproteinemia, straw colored in TB and cirrhosis, bloody or hemorrhagic in pancreatic ascites and malignancy, deep yellow or dark brown in biliary ascites, milky or chylous in TB, cirrhosis and intestinal lymphangiectasia (**Fig. 3**).

Cell count Normally the total leukocyte count is less than 500 cells/mm³ with less than 250 polymorphs/mm³. A polymorphonuclear (PMN) count greater than 250 cells/mm³ is suggestive of bacterial peritonitis.

Gram stain and acid-fast bacillus (AFB) stain In SBP, Gram's stain is not routinely required since the infection is paucibacillary with a yield rate of only 10%. However, in secondary bacterial peritonitis, neutrophils and multiple organisms are seen. AFB staining for TB rarely yields positive results.

Culture 10 mL of ascitic fluid directly inoculated into the blood culture bottles increases the positive yield of neutrocytic ascites to 80%. Polymicrobial infection is seen in secondary bacterial peritonitis while mono-microbial infection denotes SBP. There are five subtypes of bacterial ascites of which SBP, Mono-microbial non-neutrocytic bacterascites (MNB) and culture negative neutrocytic ascites (CNNA) are spontaneous bacterial infections. Secondary bacterial peritonitis and polymicrobial bacterascites occur due to an underlying pathological or procedural cause.

Serum ascites albumin gradient (SAAG) This gradient is calculated by subtracting the value of ascitic fluid albumin from the serum albumin estimated concurrently. SAAG is classified as high gradient ascites (> 1.1) and low gradient ascites (< 1.1). High gradient ascites is seen in PHT with a diagnostic accuracy of 97%. Other conditions

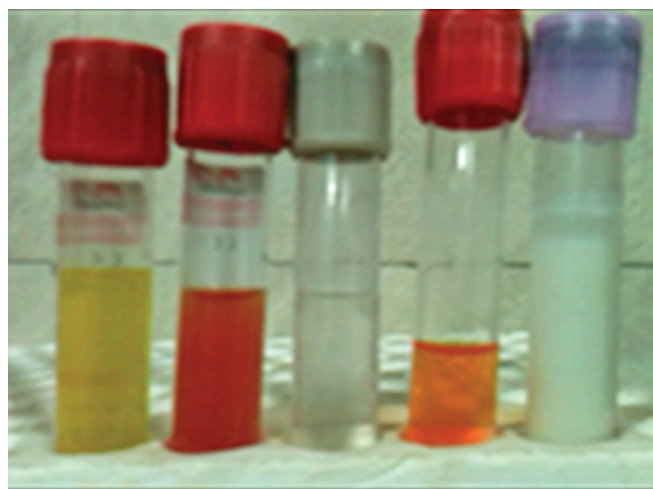


Figure 3 Color of ascitic fluid: straw, hemorrhagic, watery, xanthochromic and milky (from Left to right)

where high SAAG is seen are Budd-Chiari syndrome, portal vein thrombosis, acute liver failure and hypothyroidism. Low-gradient ascites is seen in TB peritonitis, pancreatic ascites, biliary ascites, nephrotic syndrome and serositis. SAAG may be falsely high in chylous ascites since lipid interferes with albumin estimation.

Special additional tests High amylase in ascitic fluid [(AF)/serum ratio > 0.4] indicates pancreatic ascites, urea and creatinine in AF more than the serum indicates uroascites, AF bilirubin greater than 6 mg/dL indicates biliary ascites and AF triglyceride greater than 200 mg/dL indicates chylous ascites. GeneXpert MTB/RIF test is a new molecular test for TB that detects the DNA in TB bacteria.

Complications Paracentesis is generally considered a safe procedure when performed cautiously. Complications are uncommon though infection, dyselektrolytemia, bowel and bladder perforation and large intra-abdominal hemorrhage have been reported.

Specific Investigations

Apart from basic investigations such as complete blood count, blood sugar, biochemical tests of the liver and renal function tests, additional investigations to confirm the etiology are done in children presenting with ascites. In children with short duration ascites serology for leptospirosis, dengue, *Salmonella* and markers for HAV and HEV should be done. In cirrhotic ascites, viral markers for HBV, HCV, Wilson disease work-up, auto antibodies should be included. Upper GI endoscopy is done to document varices and to perform duodenal mucosal biopsy.

MANAGEMENT

In children with non-cirrhotic ascites, definitive interventions and treatment of the underlying disease helps in the resolution of ascites. Management of cirrhotic ascites is detailed here:

Cirrhotic Ascites

Asymptomatic children with minimal ascites may not require any intervention. The weight of the child and a proper fluid intake and output chart should be monitored and recorded daily. The two components of therapy are sodium restriction and diuretics. The aim is to achieve a negative sodium balance so that the ascites decreases and then maintain a sodium balance to prevent recurrence. The management of cirrhotic ascites is shown in **Flow chart 2**.

Restriction of sodium and fluids In infants and children sodium is restricted to a maximum of 1–2 mEq/kg/day and 1–2 g/day (44–88 mEq) in adolescents. Water restriction is necessary only if serum sodium is less than 125 mEq/L.

Diuretics In cirrhotic ascites renal sodium retention is due to hyperaldosteronism. Aldosterone antagonist spironolactone is the diuretic of choice being more effective than loop diuretics in the management of ascites. The metabolites of spironolactone act on the cortical and medullary collecting tubule thereby inhibiting the binding of aldosterone.

Spironolactone is started at 2–3 mg/kg/day (max: 100 mg) given as a single dose in the morning and if necessary, increased by 2 mg/kg once in 5–7 days till the maximum dose of 4–6 mg/kg (up to 400 mg/day) is reached. The goal of therapy is to reduce body weight by 300–500 g/day until ascites resolves.

A combination of aldosterone antagonist and a loop diuretic (dual therapy) may be beneficial when there is no response with spironolactone as monotherapy, quicker response is required or recurrent ascites. Furosemide at 1 mg/kg/day (max: 40 mg) may be added to spironolactone.

Supplemental albumin When serum albumin is less than 2.5 g/dL it may be advisable to replace serum albumin since low albumin may worsen ascites.

Large volume paracentesis (LVP) Large volume paracentesis is the treatment of choice for diuretic resistant severe ascites or those with respiratory compromise. LVP is defined as removal of ascitic fluid 50 mL/kg or more of dry body weight. Studies have shown that a mean volume of 118 ± 56 mL/kg can be safely removed over one time. This is the first line treatment for tense ascites and second line treatment for refractory ascites. LVP should be done under cover of 0.5–1 g of albumin/kg or 8 g/L of AF drained.

Refractory ascites Diuretic-resistant ascites (DRA) is present if it is unresponsive to 1 week of maximum dosage of dual therapy. Diuretic-intractable ascites (DRI) is the term used when there are diuretic-induced complications that preclude the usage of an effective diuretic dosage. The various modalities of managing refractory ascites include LVP with albumin administration, continuing diuretic therapy, transjugular intrahepatic porto systemic shunt (TIPSS) and liver transplantation.

Transjugular intrahepatic porto systemic shunt Children with refractory ascites and in those awaiting liver transplantation, TIPSS acts as a bridge therapy. TIPSS lowers portal pressure and is therefore effective in decreasing ascites. Contraindications for TIPSS include severe liver failure, renal failure, sepsis and severe cardiopulmonary disease.

Peritoneovenous shunting (Leveen and Denver shunts) A conduit is created within the peritoneum for the fluid to drain into the superior vena cava via the right internal jugular vein in those with intractable ascites.

Liver transplantation This modality is the only definitive therapy for children with end stage liver disease and refractory ascites. The outcome is good if transplant is performed before the development of hepatorenal syndrome.

Newer modalities This includes atrial natriuretic peptide (ANP), terlipressin, docarpamine (an orally active prodrug), V2 receptor antagonist (OPC-3126), k-opioid antagonist (niravoline) and adenosine-1-receptor antagonist (FK352).

Prevention of SBP Since the occurrence of SBP is associated with increased mortality it is necessary to prevent SBP. Long-term oral norfloxacin at a dose of 5–7.5 mg/kg once a day is recommended.

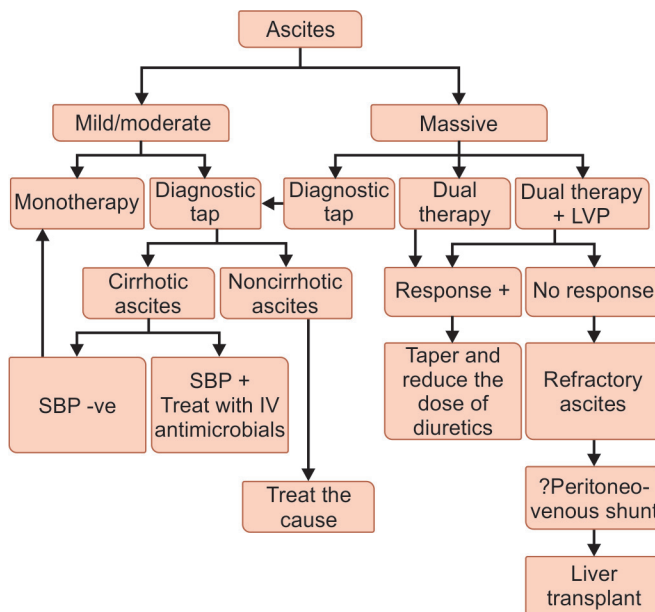
PROGNOSIS

Persisting ascites in a child with cirrhosis is a marker of decompensation. Refractory ascites and SBP are also indicators of a poor prognosis in cirrhosis.

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Flow chart 2 Management of cirrhotic ascites



IN A NUTSHELL

1. Ascites is the pathologic accumulation of fluid in the peritoneal cavity.
2. The most important cause of ascites is cirrhosis.
3. Noncirrhotic causes should be considered and identified for definitive therapy.
4. Ultrasound of abdomen is an excellent noninvasive modality for diagnosis.
5. Paracentesis is a safe diagnostic and therapeutic procedure.
6. Spontaneous bacterial peritonitis should be recognized and appropriately treated.
7. Diuretics should be administered at the proper dosage and duration for effective results.
8. Liver transplant is indicated in refractory ascites and end stage liver disease.

Chapter 35.21

Intestinal Obstruction

Ketan Parikh

Intestinal obstruction is defined as failure of effective aboral progression of the gastrointestinal contents. The initial clinical presentation is similar to various other medical conditions in children and a very high index of suspicion is therefore required. Early and effective management will help to reduce the morbidity and complications which may otherwise follow. Most cases of intestinal obstruction in children are due to congenital anomalies. However, in our country abdominal tuberculosis continues to form a recognizable cause, whereas meconium ileus and Crohn's disease which are relatively common in the west are less common.

ETIOLOGY

The failure of the aboral progression may be either due to a mechanical obstruction of the GI tract (dynamic) or the ineffective propulsive peristalsis (adynamic). The mechanical obstruction may be due to pathology of the wall of the intestinal tract, external compression of the intestinal tract; an intraluminal occlusion of the passage; or a combination of two of the above acute or chronic obstruction. Common cases are listed in **Box 1**.

BOX 1 Common causes of intestinal obstruction in children

- Intestinal atresias—duodenal, ileal, jejunal and colonic in that order of frequency
- Volvulus neonatorum due to intestinal malrotation
- Hirschsprung disease
- Anorectal malformations—not classically described as intestinal obstruction
- Intussusception
- Strangulated hernias—(external–inguinal/umbilical); Internal due to bands like persistent vitellointestinal bands, Ladd bands or other various unnamed bands and mesenteric defects
- Meconium ileus
- Inflammatory or postoperative adhesions
- Ascariasis bolus
- Tuberculous adhesions, cocoon formation, strictures
- Intestinal duplication cysts or mesenteric cysts.

PATHOPHYSIOLOGY

Once mechanical obstruction sets in, the bowel proximal to the obstruction undergoes dilatation due to the accumulated contents. There is hyper-peristalsis in an attempt to overcome the obstruction and this leads to colicky pain. If the obstruction is gradual or chronic, then this proximal bowel also undergoes hypertrophy. The persistence of obstruction and dilatation may initiate reverse peristalsis in the proximal bowel and this may cause vomiting. The dilatation of the obstructed bowel also increases the quantity of the intestinal secretions. While the pylorus normally prevents the reverse egress of the duodenal (bilious) contents into the stomach, the dilatation and reverse peristalsis of this portion of the bowel leads to bilious vomiting or gastric aspirates. The stagnant intestinal contents provide a potent medium for the overgrowth of intestinal commensals. This leads to mucosal inflammation, increased intestinal secretions and formation of increased amounts of gas.

Occasionally, the dilated proximal loop of bowel may twist or kink on itself thus creating a secondary obstruction more proximally—*closed loop syndrome*. This sequestered section which is obstructed

both proximally and distally gradually dilates due to accumulated gas and intestinal secretions with potential chances of perforation. Prior to perforation, the bowel undergoes massive dilatation with resultant ischemia of its wall. At this stage the pain is severe and usually unresponsive to most antispasmodics. Once the bowel perforates, the dilatation settles due to leakage of the contents into the peritoneal cavity and the pain settles giving a false sense of recovery. Gradually the leaked bowel contents lead to localized or generalized peritonitis and progressive deterioration of the general condition. The high gastric aspirates or the sequestered fluid in the dilated bowel lumen and the edema of the bowel wall collectively contribute to massive fluid losses (overt and covert) and electrolyte disturbances. Before perforation, infected foci may develop in the ischemic areas of the bowel wall leading to portal pyemia and rapid deterioration.

Adynamic obstruction is usually secondary to a pre-existing condition. Electrolyte disturbances, sepsis, metabolic disturbances and drugs are the few common causes. Perforation may occur secondary to a closed loop obstruction but severe fluid and electrolyte disturbances are common complications.

CLINICAL FEATURES

Children present with a variable combination of the following features: vomiting—initially nonbilious but gradually becoming bilious; abdominal distension; constipation; and abdominal pain. The mode of presentation depends on the following factors:

- *The type of obstruction:* Adynamic obstruction usually has an underlying primary pathology. Abdominal distension is a prominent feature and pain is a late symptom. Constipation may not be absolute and the patient may pass intermittent mucoid discharge with or without fecal matter.
- *The age of the patient:* In an infant, pain may manifest only as excessive crying and thus may be missed for some time.
- *The level of obstruction:* In high obstructions, the primary presentation is vomiting whereas abdominal distension may never be seen or is restricted to the upper abdomen. Additionally, the patient (even a newborn) may pass some stools but a careful history reveals that these are generally pale (mucoid). However, the patient tends to lose excessive fluids in vomiting and gastric aspirates. In lower intestinal obstructions, vomiting is a late sign whereas constipation is the primary symptom.
- *The stage of intestinal obstruction:* In patients, who present late, pain may reduce after perforation of the bowel and features of sepsis and metabolic disturbances may predominate rather than abdominal signs.

DIAGNOSIS

Bilious vomiting is the strongest clinical indicator of an intestinal obstruction. Passage of pure mucoid discharge per rectally is also a strong indicator. Abdominal colics unresponsive to oral medications and passage of blood stained mucus per rectum are warning signs of compromised bowel vascularity. Sudden fall in platelet count in a sick child may be the earliest indicator of bowel gangrene.

IMAGING

A plain vertical or lateral decubitus film of the abdomen is the most informative.

- The presence of fluid levels is indicative of obstruction; the number of fluid levels suggests the level of obstruction (**Fig. 1**).
- If the colon is also dilated, it indicates either a low obstruction or adynamic obstruction.
- A supine film (although may not show fluid levels), shows the bowel pattern better and if showing an isolated massively small bowel loop may suggest a closed loop obstruction and thus an indication for early intervention.

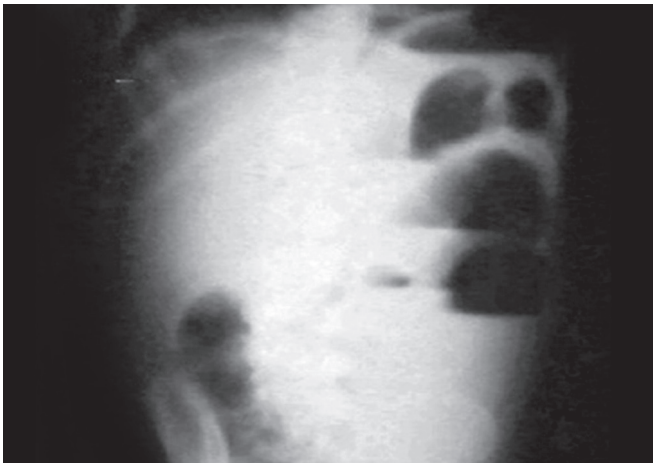


Figure 1 Fluid levels in a child with intestinal obstruction

- If the dilated bowel loops are seen in a relatively white background, it may indicate excessive peritoneal fluid/thickened (edematous) bowel wall due to peritonitis (**Fig. 2**).
- Pneumoperitoneum is a rare finding even in the presence of bowel perforation thus its absence has negligible relevance. A large pneumoperitoneum is seen only in gastric or duodenal perforations or in colonic perforations.
- Intramural air or air in the portal vein is indicative of bowel wall necrosis with gas forming bacteria.
- Air in the rectum in a case of multiple fluid levels suggests an adynamic obstruction.

Ultrasonography

Ultrasonography of the abdomen may additionally confirm the presence of fluid in the peritoneal cavity and the nature of the fluid (thick fluid suggesting pus). It may also identify pathologies like intussusception; and may identify an adynamic bowel loop. A concomitant Doppler study may indicate its vascularity. CT imaging of the abdomen is rarely done in children. It may yield information on localized inflammatory pathologies of the bowel and also help identify internal hernia.

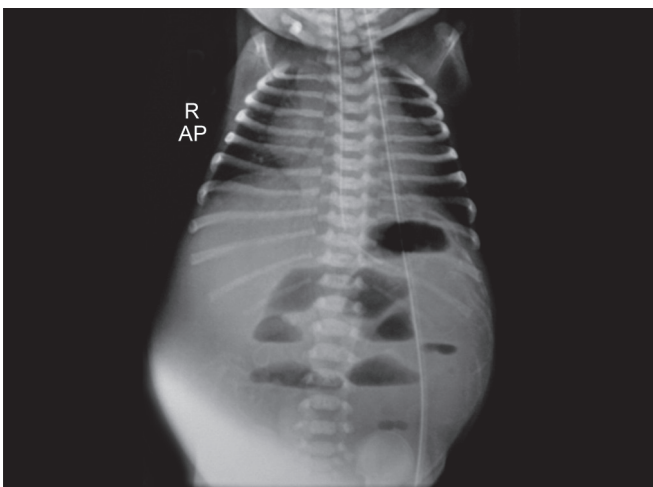


Figure 2 Fluid levels surrounded by ground glass appearance—peritonitis

MANAGEMENT

Most children with intestinal obstruction are given a trial of conservative management, traditionally referred to as *drip and suck*. This involves keeping the patient nil orally and intravenous supplementation along with a regular deflation of the proximal GI tract with regular aspiration through a nasogastric tube. It decreases the pressure on the bowel wall, reducing the edema and may result in opening out the narrowed portion of the bowel. Supplementation of electrolytes and judicious use of antibiotics are necessary in most cases. The indications for surgery are listed in **Box 2**.

BOX 2 Indications of surgery in intestinal obstruction

- Suspicion of closed loop obstruction (fear of perforation)
- Volvulus neonatorum
- Suggestion of strangulated hernia
- Any suggestion of perforation
- Suggestion of peritonitis
- Any suggestion of vascular compromise of section of bowel
- Associated peritonitis
- Failure of conservative treatment.

OUTCOME

The outcome depends primarily on the nature of the obstruction and the associated complications, if any. In most cases of pure obstruction with negligible complications, the outcome is excellent even if surgical correction is required. Presence of sepsis and associated comorbidities may affect the final outcome.

IN A NUTSHELL

1. In children with bilious vomiting, intestinal obstruction should be suspected.
2. Abdominal pain which is not relieved with antispasmodics should raise a suspicion of compromised bowel vascularity.
3. Non-feculent passage of blood or mucus per rectum should raise the possibility of intestinal obstruction in a child with acute abdomen.
4. A vertical plain film of the abdomen is the single most helpful imaging modality.

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Chapter 35.22

Intussusception

Ketan Parikh

Intussusception is characterized by the telescoping of one part of the intestine into another (**Fig. 1**). Even though it may occur at any age, the most common age of presentation is 8–10 months. Hence, rotavirus infection may play a role.

ETIOLOGY

- **Idiopathic** This is the most common variety of intussusception and occurs in the infant. It is usually linked with the period of weaning.
- **Secondary intussusceptions** Occur due to an intraluminal pathology or growths like polyps, submucosal masses, etc. (**Fig. 2**) which act as lead points. Submucosal hematomas seen in Henoch-Schönlein purpura may also contribute.

PATHOGENESIS

The most common site of the idiopathic variety is the ileocecal region, and the most common lead point is a hypertrophied Peyer's patch. This hypertrophy occurs due to a change in the bacterial flora during weaning or gastrointestinal infection or following ingestion of infected respiratory secretions. The telescoped bowel carries with it its attached mesentery. The resultant compression of the mesentery progressively leads to lymphatic and venous congestion of the involved segment of the bowel and finally arterial compression. The congested and hyperemic mucosa of the innermost layer of intussusception causes secretion of blood and mucus, characteristically labeled as *red currant jelly stool*. Further vascular compromise may then lead to gangrene of a portion of the bowel (**Fig. 3**).

CLINICAL FEATURES

Disease usually occurs in a classically healthy, well-nourished child, less than one year of age. There may be a prior history of an upper respiratory tract infection. Colicky pain occurs in short bursts with intermittent periods of remission. Vomiting is bilious only in late cases. The hallmark of diagnosis is red currant jelly stools—usually with no fecal matter (a differentiating feature from dysentery) (**Fig. 4**). On abdominal palpation, intussusception may be felt as a banana-shaped mass with the concavity towards the umbilicus. Occasionally, the mass can be felt per rectally. In late cases, features of septicemia and peritonitis may be seen.

DIFFERENTIAL DIAGNOSES

Intussusception is very commonly mistaken for dysentery and hence the diagnosis may be delayed. In intussusception, the stool contains mainly blood and mucus without fecal matter. Intestinal obstruction (fluid levels) and peritonitis are very late signs and one should never wait for them to appear.

APPROACH TO DIAGNOSIS

Clinically, a palpable (banana shaped) bowel mass is suggestive. Ultrasound of the abdomen can be diagnostic (**Fig. 5**). It shows the *pseudo-kidney* sign or the *bowel-in-bowel* sign. A Doppler study performed simultaneously may indicate the blood flow to the portion. Alternatively, a barium enema may show the *coiled spring* sign or the *claw sign* (**Fig. 6**). Laboratory studies may show evidence

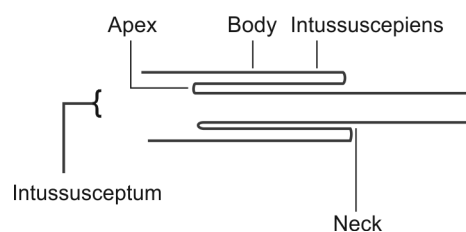


Figure 1 Diagrammatic representation of parts of intussusception

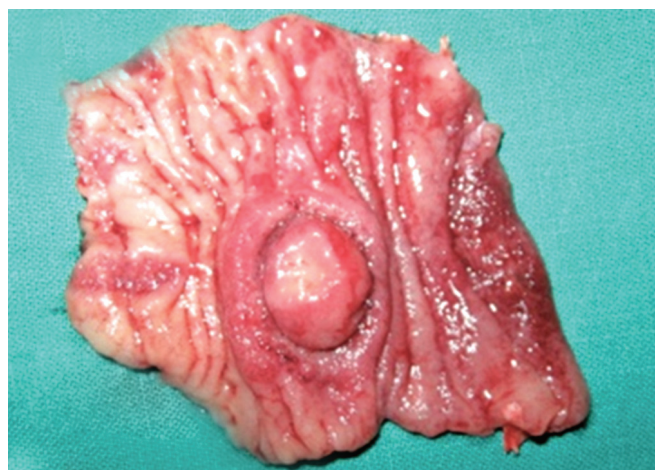


Figure 2 Luminal sessile polyp, a lead point for a secondary intussusception

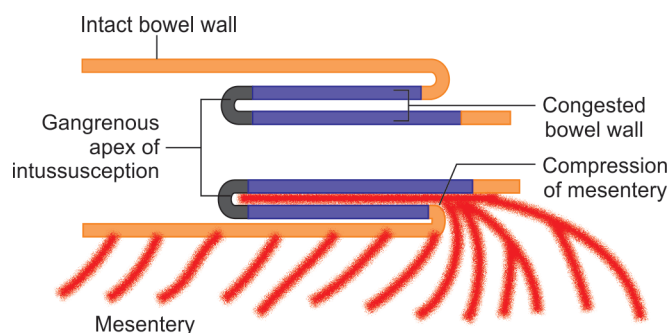


Figure 3 Diagrammatic representation showing the compression of the mesentery and resultant mucosal ischemia



Figure 4 Rectal bleeding without fecal matter

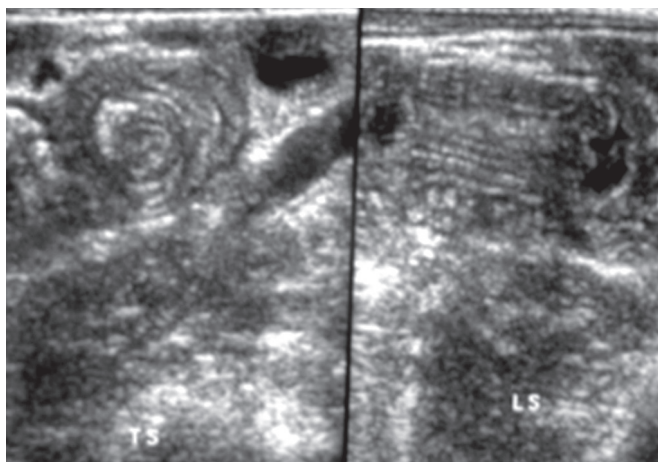


Figure 5 Ultrasonographic picture of intussusception



Figure 6 Barium enema showing *coiled spring sign*

of blood loss, dehydration and electrolyte imbalance. A CT scan is rarely indicated except in cases where there is excessive gas in the bowel loops which precludes a good sonographic assessment.

MANAGEMENT

Once suspected, the patient should be kept nil orally and a nasogastric decompression initiated as soon as possible. Correction of metabolic disturbances, including intravenous supplementation of fluid should be started before attempting any hydrostatic reduction. If necessary, blood transfusion may be started along with broad-spectrum and antianaerobic antibiotics.

Definitive Treatment

If diagnosed within 24 hours of onset, hydrostatic reduction (under sonographic or radiological control) may be attempted by a pediatric surgeon, with facilities for immediate surgery kept ready in case of complications. *It is important that any patient taken up for hydrostatic reduction should be ready to be taken to the operation theater immediately in case of a leak or perforation.* Therefore, such a procedure must be undertaken only in the presence of a surgeon after initial resuscitation of the patient. Reduction may be attempted under laparoscopic monitoring in those patients where bowel vascularity is suspect. If hydrostatic reduction fails or is contraindicated, exploratory laparotomy with operative reduction or if necessary, resection and anastomosis may have to be undertaken.

IN A NUTSHELL

1. Intussusception is one of the most common abdominal emergencies in infants with disastrous consequences, if not treated in time.
2. In any infant with severe colicky pain or bleeding per rectum, intussusception should be ruled out.
3. A good ultrasonographic evaluation is reasonably reliable to diagnose intussusception.
4. Hydrostatic reduction should not be initiated on an out patient basis without intravenous resuscitation.

MORE ON THIS TOPIC

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Chapter 35.23

Appendicitis

Prakash Agarwal

Appendicitis is a medical emergency that requires prompt surgery. It is one of the most common acute surgical problems in children and is most commonly misdiagnosed. Left untreated, an inflamed appendix will eventually perforate leading to peritonitis. The incidence of appendicitis varies worldwide. In India more than 2,70,000 cases are reported annually. Although it can strike at any age, appendicitis is rare under age 2 and most common between ages 10 and 30.

ETIOLOGY

Appendicitis may be a result of luminal obstruction followed by infection due to *Yersinia*, *Salmonella* and *Shigella*. The cause of luminal obstruction may be an inspissated and calcified fecal mater (fecalith). Appendiceal lymphoid hyperplasia may cause luminal obstruction leading to appendicitis. Parasitic infection such as *Entamoeba*, *Strongyloides*, *Enterobius vermicularis*, *Schistosoma* or *Ascaris* can cause appendicitis. Enteric and systemic viral infection can also lead to appendicitis.

PATHOGENESIS

Spectrum of appendicitis evolves from a simple infection to perforation. The varying stages of appendicitis include acute appendicitis, suppurative appendicitis, gangrenous appendicitis and perforated appendicitis.

CLINICAL FEATURES

The child may complain of vague gastrointestinal symptoms before classical presentation sets in. There may be anorexia, indigestion or change in bowel habits. Initially the child may complain of pain around the umbilicus which gets localized to the right iliac fossa. The continuous inflammation of the appendix will cause distention of the appendiceal wall leading to nausea and vomiting. After a few hours of nausea and vomiting, pain sets in. As the pressure inside the inflamed appendix increases, the lymphatics get obstructed, leading to further edema and swelling. Further increase in pressure leads to venous congestion resulting in ischemia, infarction and gangrene. This leads to bacterial transmigration of the wall of appendix. As a result of mediators released by ischemic tissue, white blood cells and bacteria, child develops fever, tachycardia and leukocytosis.

An inflamed appendix coming in contact with the parietal wall triggers off pain localized in the right iliac fossa or the McBurney's point. Further increase in intraluminal pressure will lead to perforation, localized abscess formation, if omentum conceals the perforation or it may lead to generalized peritonitis. Signs of acute appendicitis are fever more than 101°F, high leukocyte count and tachycardia with tenderness in the McBurney's point. A pelvic abscess due to perforated appendix may lead to diarrhea, or tenesmus.

Younger children usually present with a complicated appendicitis because of inability to give proper history and low index of suspicion by the clinician. The most common presenting symptoms for these children will be vomiting, followed by fever and abdominal pain.

DIAGNOSIS

Appendicitis can mimic a variety of intra-abdominal conditions (**Table 1**). The clinical diagnosis of appendicitis is challenging and may be mistaken for acute gastroenteritis, viral mesenteric adenitis, Meckel diverticulitis and Crohn's disease. Extra-abdominal causes like pleurisy and pneumonia can mimic acute appendicitis.

Physical Examination

Clinically, a child with appendicitis will be quite and lie in bed with minimal movement. An older child may limp while walking with a grumpy face. They will give history of pain with every jerk while walking or coughing. If the child is asked to show the area of pain, they will usually point to the McBurney's point.

Palpation should be started away from the site of tenderness and progressed towards the site of pain. This will help in eliciting the Rovsing sign which indicates peritoneal irritation due to referred pain. A classical McBurney's point tenderness is diagnostic of acute appendicitis in conjunction with an elevated total leukocyte count, tachycardia and fever. Tenderness may be mild during the initial stages and can be elicited by palpation or percussion. The pain of retrocecal appendix may be elicited midway between the 12th rib and posterior superior iliac spine. Rectal tenderness will suggest a pelvic appendicitis.

A perforated appendicitis may present in the form of local or generalized guarding and rigidity, depending on the severity of the disease. Rebound tenderness may indicate localized peritonitis. If the diagnosis is in doubt, serial abdominal examination at intervals of 6–12 hours can be helpful.

Imaging

A plain X-ray may suggest fecaliths in 10–20% of cases but is rarely done. A chest X-ray to rule out pneumonia may be needed. An ultrasound may suggest a noncompressible appendix with an AP diameter of more than 7 mm. Presence of an appendicolith, with periappendiceal fluid may be confirmatory in the hands of a skilled radiologist. CT scan may show an enlarged appendix with thickening of the appendiceal wall, periappendiceal fat stranding

Table 1 Differential diagnosis of acute appendicitis

Gastrointestinal system	Acute gastroenteritis Acute viral mesenteric adenitis Constipation Meckel diverticulitis Crohn's disease Typhoid Appendiceal tumor, carcinoid tumor
Hepatobiliary	Hepatitis Cholecystitis
Urinary system	Hydronephrosis Pyelonephritis Ureteral or renal calculus
Uterus, ovary	Ovarian torsion Ruptured ovarian cyst
Others	Primary peritonitis Henoch-Schönlein purpura Pancreatitis Pleuritis Pneumonia Psoas abscess Torsion of appendix epiploica

and enhancement of appendiceal wall. It may help in the diagnosis due to anatomical abnormality such as malrotation or situs inversus. The sensitivity of CT scan is over 90% and its specificity is over 80%. Serial examination by the same examiner is the safest and the most accurate diagnostic tool.

Hematology

Leukocytosis with neutrophilia and increased CRP may be seen but are not diagnostic.

MANAGEMENT

In early noncomplicated appendicitis only perioperative antibiotics are required.

The gold standard treatment for appendicitis is prompt surgery. Majority of the appendicitis today are operated by laparoscopic methods (**Fig. 1**). Open appendectomy is becoming rarer in surgical practice though the trainee should be aware of it if having problems in performing laparoscopic appendectomy. The advantages of laparoscopic appendectomy are many fold including shorter hospitalizations, better scar, decreased

postoperative pain, decreased wound complications, increased ability to diagnose coexisting conditions or other pathological conditions, surgical ease in obese patients and faster postoperative recovery. Laparoscopic appendectomy for complicated appendicitis is becoming popular.

If not treated in time acute appendicitis may lead to complications like perforation and peritonitis. With the advent of higher antibiotics and awareness there is a decline in the incidence of complications. Complications of appendicitis include wound infection, intra-abdominal abscess formation, postoperative intestinal obstruction, prolonged ileus and enterocutaneous fistula. Acute appendicitis in females should be treated with a low threshold for surgery as complicated appendicitis may lead to fertility problems in the future.

In recent years due to broad spectrum antibiotics the mortality due to complicated appendicitis is almost nil. Antibiotics have markedly decreased the incidence of various complications listed above. Although the length of hospitalization and morbidity due to complicated appendicitis still far exceeds those with simple appendicitis, the overall morbidity in children with complicated appendicitis is less than 10%.



Figure 1 Laparoscopic view of a case of acute appendicitis

IN A NUTSHELL

1. Appendicitis remains the most common acute surgical condition of the abdomen in children.
2. Luminal obstruction due to fecalith remains the most common cause of acute appendicitis.
3. Salient clinical features of acute appendicitis are—right iliac fossa pain, nausea and vomiting, fever associated with tachycardia and elevated leukocyte count.
4. The gold standard treatment for appendicitis is laparoscopic appendectomy.

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Chapter 35.24

Testicular Torsion

Prakash Agarwal

Torsion of the testis is a surgical emergency which results in occlusion of the gonadal blood supply. If unrelieved within hours it may lead to necrosis. It occurs usually in fully descended testis but may be seen in undescended testis as well. Previously the incidence of torsion in an undescended testis was very high. However due to the present practice of earlier surgical intervention torsion in an undescended testis is now rare.

PATHOGENESIS

Torsion may be intravaginal or extravaginal. Intravaginal torsion is more common due to high investment of the spermatic cord by the tunica vaginalis. Extravaginal torsion is less common and confined to the perinatal period.

In *intravaginal torsion*, the long narrow mesorchium allows the testis to lie horizontally rather than fixed vertically as in the normal testis. The pendulous testis with a high investment of the cord has a horizontal lie and allows the testis to be readily twisted by cremasteric contractions or by a jerky movement. This phenomenon is seen more commonly in undescended testis.

In *extravaginal torsion* there is a loose areolar plane around the moving gubernaculum and testis into the scrotum, which allows the entire testis and spermatic cord to twist. Beyond the newborn period testicular torsion is almost always associated with the bell clapper deformity. Cremasteric contraction may be either the cause or the effect of torsion. The high incidence of testicular torsion in puberty is due to the increased levels of testosterone making the testis bulky and more prone for torsion. The most common age for torsion of the testicular appendix is around 11 years. This peak, just before the onset of puberty may be related to early pubertal stimulation by estrogen. Chances of necrosis of the testis are less, if the number of twists is less or there are chances of spontaneous untwisting. In adolescent boys necrosis may occur after as early as 2 hours and very likely after 24 hours. The testis has four testicular appendages of which the hydatid of Morgagni is the most frequently twisted.

CLINICAL FEATURES

Torsion of the testis is commonly seen in the adolescent age group but the testicular appendage torsion is seen before puberty. Usually there are two peaks of torsion of the testis: in the early neonatal period and in adolescent boys aged 13–16 years. Usually testicular torsion is heralded by the sudden onset of pain in the testis, lower abdomen or groin, associated with nausea and vomiting. The hemiscrotum looks red and edematous (**Fig. 1**) and if untreated leads to a bluish discoloration of the scrotum. In torsion of a testicular appendage, a bluish black spot (blue-dot) may be seen through the skin at the upper pole of the testis. This is more prominent in the white population compared to dark skin people. Palpation of this area causes extreme pain, whereas the rest of the testis is not so painful. Once secondary inflammation and edema of the scrotum occur, it may be impossible to distinguish between testicular torsion and torsion of a testicular appendage.

DIAGNOSIS

Inflammatory conditions of the scrotum like epididymo-orchitis, epididymitis may mimic torsion testis. Idiopathic scrotal edema, fat



Figure 1 Red and edematous hemiscrotum in torsion of testis

necrosis and mumps orchitis are the other differential diagnoses. Radioisotope scan and Doppler ultrasound has been used to determine whether there is blood flow to the testis or not. These tests may be more useful after puberty as the testicular volume is greater after puberty. However, exploration is recommended for all doubtful cases of acute scrotum.

MANAGEMENT

Treatment of torsion of the testis is immediate operative exploration of the scrotum. The hemiscrotum is opened in the midline with a diathermy. The testis is delivered through the incision, and inspected. If the testis is twisted it is untwisted and the viability is assessed. If the torsion is early the circulation may return within few minutes. If there is congestion, then it may be better to observe the testis for several minutes by giving warm packs and asking the anesthetist to give 100% oxygen. If there is no improvement in the viability of the testis then an orchidectomy is done by double ligation of the testicular vessels. If the testis appears viable, no further treatment is required. The appendage testis is inspected and excised, if there is torsion. In case of epididymo-orchitis removal of the edematous fluid leads to relief of symptoms. Exploration of the contralateral testis is usually done since the anomaly is bilateral and the testis is fixed in all cases which required orchidectomy.

OUTCOME

The management of a testis of doubtful viability on operation is controversial. Leaving behind such a testis is to see if they will recover any hormonal function. However it has recently been reported that children older than 10 years of age are at risk of developing antisperm antibodies. It has been seen that men who underwent fixation of ischemic testes at adolescence had poor spermatogenesis later in life. Some authors therefore recommend preservation of a doubtful testis if the boy is below 10 years and orchidectomy for those above that age.

PREVENTION

Adolescents should be made to report sudden acute or recurrent testicular pain. Prophylactic bilateral orchidopexy may be justified, especially if there is a horizontal lie of the testes on clinical examination.

IN A NUTSHELL

1. Torsion testis is a surgical emergency with a high incidence of gonadal necrosis if not treated early.
2. Torsion of the appendage of testis, epididymo-orchitis and acute scrotal edema are differential diagnosis.
3. Doppler ultrasound may suggest a reduced flow in cases of torsion but is not reliable in prepubertal children, since their testicular volume is less.
4. Diagnosis is clinical and treatment is immediate exploration. All doubtful cases also require exploration.

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Chapter 35.25

Inguinal Hernia

Prakash Agarwal

Protrusion of abdominal viscus through the patent processus vaginalis in children is termed as hernia. It is one of the most common elective surgeries performed in children. The highest incidence is in premature infants (16–25%). Inguinal hernia is commonly seen during the first year of life, with a peak incidence in the first few months. Male to female ratio is between 3:1, and 60% of the hernias are right sided. In males, this is possibly the result of the later descent of the right testicle than the left. Bilateral hernias occur in 10% of cases (**Fig. 1**). Approximately 11.5% of patients have a family history of hernia.

PATHOGENESIS

Indirect inguinal hernia is the result of failure of the processus vaginalis to close. The processus vaginalis is an invagination of the peritoneum through the internal ring through which the testis passes from the 7th month to 9th month of gestation. In females the canal of Nuck corresponds to the processus vaginalis and communicates with the labia majora. Reduced release of calcitonin gene-related peptide (CGRP) has been implicated in the formation of hernia and hydrocele.

Incarcerated hernias result from entrapment of intestine, appendix, tubes and ovaries in females or other viscera within the hernia sac. If the hernia is not reduced, strangulation may occur, and blood supply to the incarcerated organ may be reduced to the point of gangrene. The patient may present with signs of peritonitis. Incarceration is seen commonly in infants below 6 months.

CLINICAL FEATURES

Parents complain of noticing a bulge in the groin, labia or scrotum. Hernias may be seen at birth or even months after birth. They are usually asymptomatic and appear during crying, coughing or conditions due to raised intra-abdominal pressure. On examination a bulge may be seen and palpated in the inguinal region over the spermatic cord. If it is not present, the spermatic cord may be palpated to determine thickening-silk string sign. A positive sign indicates thicker cord structures within the inguinal canal compared with the normal side. If a hernia is not seen on



Figure 1 Bilateral inguinal hernia in a boy

physical examination, the history given by parents can be taken as a strong evidence for operating on the child. Obstructed hernia may lead to intermittent pain and irritability, abdominal distention, vomiting and obstipation.

DIAGNOSIS

Inguinal hernia is a clinical diagnosis made by history and physical examination. Plain X-ray abdomen if done, may show bowel loops in the scrotum. Ultrasound of the inguinal region can demonstrate herniation of omentum or bowel loops intermittently. It has gained popularity as an adjunct to physical examination. It is noninvasive and has an accuracy of 97%.

SURGERY

Herniotomy is advised at the earliest, since it will not resolve spontaneously. In young infants it should be performed immediately as the chances of obstruction are very high. Most children are operated under general anesthesia as day care surgery except premature infants who are prone for apneic spells. The repair is done with absorbable sutures which do not need removal later.

Laparoscopic repair in children has been controversial. Advantages include minimal handling of the vas, less pain, earlier return to school, repair of bilateral hernias through the same ports and easier repair of recurrent hernias. Disadvantages include longer operating time and a prolonged learning curve for the surgeons and increased cost. Laparoscopy involves insertion of 3 X 5 mm ports, correct identification of the side of hernia, excising the hernial sac and purse string intracorporeal suturing and closing the hernial sac.

Since patients presenting with left sided hernias are more likely to have bilateral hernias. Many surgeons recommend routine exploration of the opposite side. In such situations laparoscopy has the advantage of allowing direct visualization of the contralateral internal ring and repairing it at the same time.

Postoperative complications Some children may develop scrotal swelling in the postoperative period, which resolves spontaneously. Acquired undescended testis after hernia repair is an uncommon complication. Recurrence after hernia repair is reported in less than 1% of children with uncomplicated hernia, but may be as high as 15% in premature infants and 20% in incarcerated hernias. Accidental transection of the vas during surgery should be repaired immediately.

IN A NUTSHELL

1. Inguinal hernia is commonly in the first year of life, with higher incidence in premature infants.
2. The most common cause of indirect inguinal hernia in children is a patent processus vaginalis.
3. Inguinal hernia is a clinical diagnosis and surgical repair is recommended at the earliest.
4. Surgery is a day care procedure except in premature infants who are prone for apneic spells.

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Section 36 DIARRHEAL ILLNESSES

Section Editor AK Patwari

Chapter 36.1

Acute Watery Diarrhea

AK Patwari

Diarrhea remains the second leading cause of death globally among under-5 children. Despite a clear understanding regarding pathophysiology of diarrheal diseases and availability of a simple, inexpensive and effective intervention, i.e., oral rehydration therapy (ORT), acute diarrhea (AD) continues to kill children as a result of dehydration and its consequences. Repeated and prolonged episodes of diarrhea have even more deleterious effects and may eventually result in growth failure, intercurrent infections and problems associated with severe malnutrition and even death.

EPIDEMIOLOGY

The global annual burden of diarrhea is huge, causing 11% or 801,000 deaths among children less than 5 years of age. Most deaths occur in children of rural background in developing countries especially in Africa and South Asia due to limited access to safe drinking water, sewage disposal and health-care and reduced opportunities for personal sanitation, hygiene, and safe food preparation. Introduction of ORT has revolutionized management of diarrhea with significant reduction in diarrhea-related mortality, but the morbidity has not decreased substantially with each child less than 5 years of age experiencing an average of 3 (range 2.8–6.3) episodes of diarrhea annually. Recent data estimates roughly 20 episodes of moderate to severe diarrhea each year per 100 children under the age of 2 years (roughly one episode per five children each year). Infants are reported to have highest burden (30 cases per 100 children each year).

ETIOLOGY

In developing countries, the organisms most frequently associated with acute watery diarrhea include enterotoxigenic *Escherichia coli* (ETEC), enteropathogenic *Escherichia coli* (EPEC), *Shigella* and *Campylobacter jejuni*. Rotavirus is a common cause of severe diarrhea, vomiting and fever leading to rapid dehydration. *Vibrio cholerae* is an important organism in endemic areas and during epidemics. Nontyphoidal *Salmonella* is a common organism in areas where commercially processed foods are widely used and in hospital outbreaks. Most of these organisms cause watery diarrhea. Results of global enteric multicenter study (GEMS) report rotavirus, *Cryptosporidium*, *Shigella* and enterotoxigenic *E. coli* (specifically ST-ETEC) as most common pathogens to cause moderate to severe diarrhea (**Table 1**). Diarrhea may also be caused by antibacterial agents like ampicillin, cotrimoxazole, chloramphenicol, amoxicillin, and clindamycin. Pseudomembranous colitis is the most severe form of antibiotic associated diarrhea.

PATHOGENESIS

Most enteropathogens cause diarrhea by more than one mechanism. The clinical presentation depends upon the underlying pathophysiological changes taking place in the gastrointestinal tract (GIT). Three clinical types of diarrhea have been defined, each reflecting a different pathogenesis and requiring different approach to treatment.

Secretory Diarrhea

It is characterized by acute watery diarrhea with profound losses of water and electrolytes due to sodium pump failure as a result of the action of identified toxins. This group is at risk for rapid development of dehydration and electrolyte imbalance. Common causes are ETEC and *V. cholerae*.

Invasive Diarrhea (Dysentery)

Intestinal mucosal cells are actually invaded by the microorganisms which setup an inflammatory reaction clinically presenting with blood and mucus in the stools. This group is prone to develop other complications like intestinal perforation, toxic megacolon, rectal prolapse, convulsions, septicemia and hemolytic uremic syndrome.

Osmotic Diarrhea

Injury to enterocytes may result in brush border damage and epithelial destruction leading to decreased mucosal disaccharidase activity. Clinical presentation is characterized by passage of large, frothy, explosive and acidic stools. High osmolar solutions given orally [e.g., carbonated soft drinks and oral rehydration solution (ORS) with high sugar content] can also result in osmotic diarrhea. Another complication of osmotic diarrhea is hypernatremia.

PATHOPHYSIOLOGY

Secretory Diarrhea

In healthy adults, around 1–1.5 liters of water are ingested daily in different forms which increase to about 9 liters by the time it reaches the jejunum (**Fig. 1**). From the jejunum, around 8 liters of water is reabsorbed along with Na^+ and Cl^- ; and K^+ and HCO_3^- are secreted into the lumen. Colon receives 1–1.5 liters of water of which more than a liter is reabsorbed along with Na^+ and Cl^- ; and K^+ and HCO_3^- secreted in to the lumen.

Absorptive Processes for Na^+ in Intestinal Epithelium

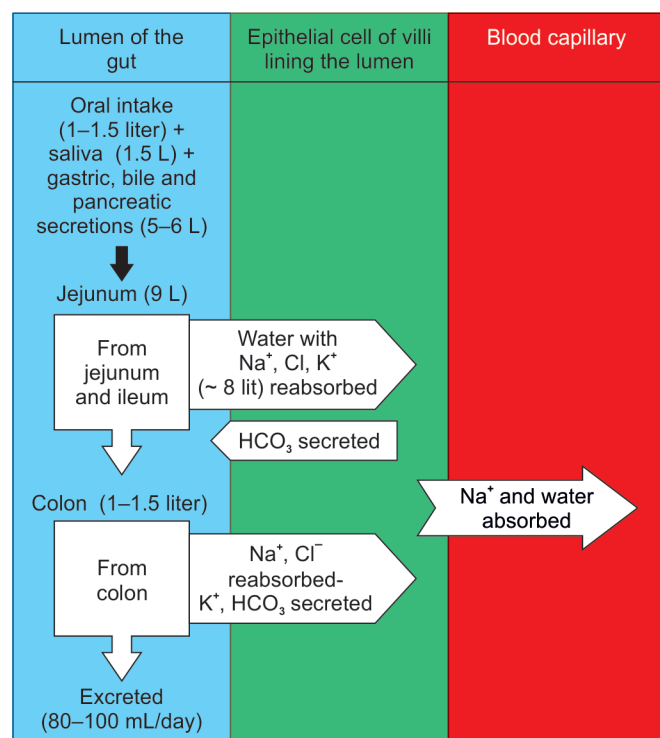
There are several pathways in the intestinal lumen which facilitate absorption of sodium and water into the capillaries thereby maintaining hydration. These pathways include glucose linked Na^+ absorption, direct absorption of Na^+ and Cl^- , Na^+ absorption in exchange for H^+ and bidirectional absorption and secretion of Na^+ and Cl^- (**Fig. 2**).

Table 1 Common pathogens for acute diarrhea in under-5 children

*Indian data (all cases of acute diarrhea)		**Multicentric data from Africa and South Asia (moderate to severe cases of diarrhea)			
Pathogen	Percentage isolated	Pathogen	Percentage isolated		
			0–11 months	12–23 months	24–59 months
Rotavirus	48.1	Rotavirus	27	25.4	14.5
<i>Vibrio cholerae</i> O1	16.4	<i>Cryptosporidium</i>	11.8	8.4	-
<i>Giardia</i>	14.2	Enterotoxigenic <i>E. coli</i> (specifically ST-EPEC)	3.0	5.8	6.1
EAEC	12	<i>Shigella</i>	2.0	7.2	12.1
Adenovirus	11.6	Norovirus	-	4.7	-
<i>Cryptosporidium</i>	11.1	Adenovirus	4.0	4.5	-
<i>C. jejuni</i>	9.3	<i>V. cholerae</i>	-	3.4	7.6
<i>Shigella</i>	7.9	<i>Campylobacter</i>	-	-	9.9
<i>E. histolytica</i>	4	<i>Sapovirus</i>	-	-	3.5

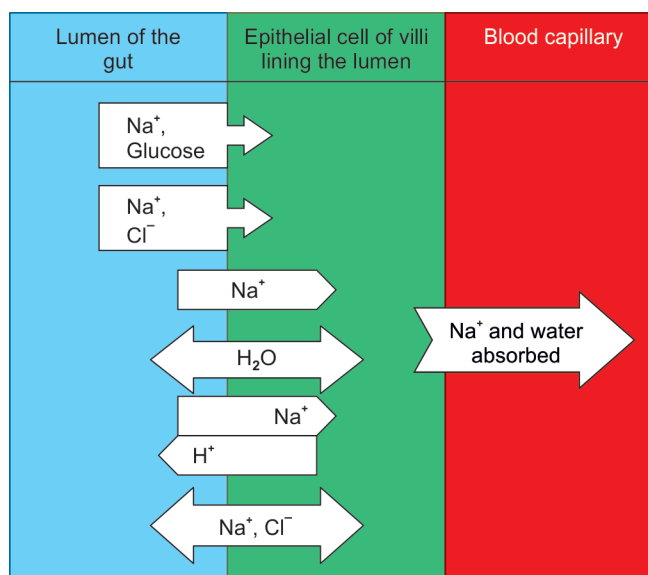
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**Figure 1** Normal absorption of water and electrolytes from the gut

Sodium Pump Failure

Organisms causing secretory diarrhea (*E. coli*, *V. cholerae*) generate several toxins that get attached to the intestinal epithelium and activates ATPase which in turn breaks down in to cyclic adenosine monophosphate (CAMP). These changes results in *sodium pump failure* which leads to disruption of proper absorption of water by opening the chloride channels responsible for releasing water from the crypts. CAMP acts on all the pathways of Na^+ absorption from the lumen, except glucose linked Na^+ absorption, and results in less absorption of Na^+ and increased secretion of Cl^- . This is followed by water, K^+ and HCO_3^- flowing into the lumen. These

**Figure 2** Absorptive processes for Na^+ in intestinal epithelium

changes lead to copious watery stools with Na^+ , K^+ and HCO_3^- (Fig. 3).

Scientific Basis of Oral Rehydration Therapy

As mentioned earlier, CAMP acts on all the pathways for absorption of Na^+ and water from the gut except glucose linked Na^+ absorption. In such a situation if a solution of water and Na^+ is given to the child, it will not be absorbed from the gut because of the blocked pathways. The unabsorbed water is excreted in addition to the diarrhea stools, thereby worsening the diarrhea. On the other hand if Na^+ and glucose are added to water in appropriate proportion, glucose linked absorption of Na^+ takes place effectively. ORT optimizes this pathway for quick replacement of losses of water and electrolytes and prevents and treats dehydration till the time effect of CAMP wanes off and all blocked pathways are opened (Fig. 4).

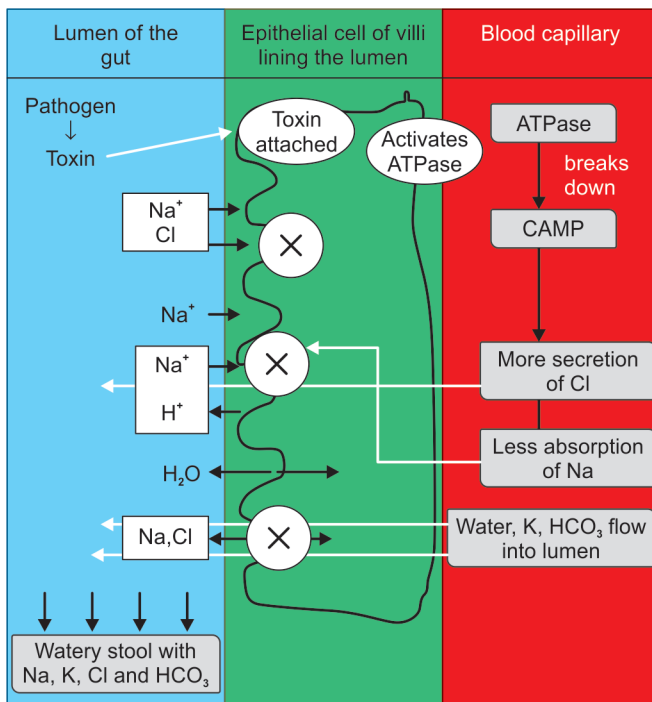


Figure 3 Pathophysiology of secretory diarrhea

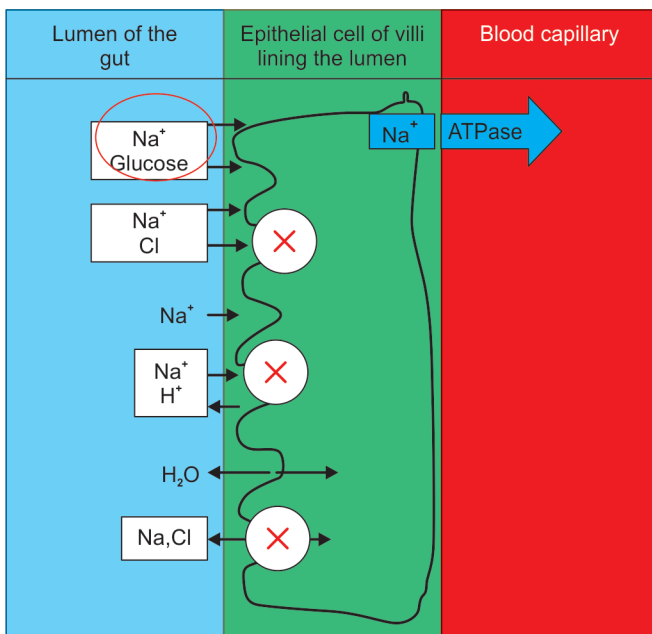


Figure 4 Glucose linked sodium absorption in acute diarrhea

Pathophysiology of Diarrheal Dehydration

Dehydration, due to loss of water and electrolytes in the stools, is the most common life-threatening consequence of diarrhea. Young children are more susceptible to develop dehydration due to limited urinary concentration capacity of the kidneys, more insensible losses of water through skin and lungs owing to large surface area and rapid breathing, and their dependence on adults to replace their fluid losses.

Loss of water and electrolytes in the diarrheal stool results in depletion of the extracellular fluid volume (ECFV), electrolyte imbalance and clinical manifestation of dehydration. Even

though intracellular and extracellular fluid compartments are equally depleted in diarrhea, the measurement of ECFV shows mostly a depletion of this compartment. The reason is that ECFV contracts in *two directions*—out in the stools and into the cell, so that the net measured loss of volume appears to come chiefly from the ECFV. Continued ECFV contraction is at the root of all the physiological changes taking place in dehydration and reversion to normal is more readily accomplished by solutions more nearly approximating that of the ECF.

The first symptom of dehydration appears after fluid loss of 5% of body weight. When fluid loss reaches 10%, shock often sets in, and the cascade of events that follows can culminate in death unless there is immediate intervention to rehydrate. In the past, higher mortality reported soon after admission, was mostly due to uncorrected volume depletion or electrolyte imbalance. These observations highlight the importance of the *first day* in the fluid therapy of severe dehydration and the need for prompt replacement of losses which if uncorrected will result in rapidly progressing dehydration, metabolic acidosis and other electrolyte imbalances.

Compensatory Mechanisms

Contraction of the ECFV consequent upon loss of water and electrolytes in diarrheal stools, leads to increase in renin, angiotensin, aldosterone and antidiuretic hormone (ADH), and fall of glomerular filtration rate (GFR). All these changes lead to compensatory retention of salt and water but proportionately more of the later. The first palpable response to ECFV contraction is thirst and if water is administered, it will be mostly retained due to the effect of ADH. In addition, water may also be generated internally by steroids and catecholamine. Therefore, retention of water by these mechanisms results in isotonic or hypotonic dehydration. Pre-existing or uncorrected potassium deficiency can also perpetuate hypotonicity. Comparison of various intravenous (IV) regimens containing high or low sodium have shown that rational treatment should reverse all the compensatory events by restoring volume quickly, correcting acidosis and reducing potassium deficit with solutions approximating the composition of the ECF. The more hypotonic the fluid is with respect to sodium, the less well it can quickly correct the ECFV contraction.

CLINICAL FEATURES

Diarrhea is usually defined as passage of three or more loose or watery stools in a 24-hour period, a loose stool being one that would take the shape of a container. However, for practical purposes, it is the recent change in consistency and character of stool and its water content rather than the number of stools that is important. Infants who are exclusively breastfed normally pass several soft or semiliquid stools each day; for them, it is practical to define diarrhea as an increase in stool frequency or liquidity that is considered abnormal by mother.

Acute watery diarrhea refers to diarrhea that begins acutely, lasts for less than 14 days, with passage of frequent loose or watery stools without visible blood. Vomiting may occur and fever may be present. Loss of large volume of water and electrolytes can result in dehydration and dyselectrolytemia.

Classification of Dehydration

Old textbooks described severity of dehydration, based on percentage of loss of body weight, as mild (< 5%), moderate (5–10%) and severe (> 10%). However, in the absence of information on premorbid weight of the child for estimating loss of body weight, it is often difficult to use weight loss as a criterion for assessment of dehydration. Moreover, thirst and irritability are the earliest

symptoms which appear when an infant has already lost almost 4–5% of body weight. Therefore by the time signs of dehydration appear the child already has mild-to-moderate dehydration. Extreme degree of dehydration presents with alteration in consciousness, shock, acidosis and renal failure. A number of clinical signs and symptoms can help in detecting dehydration. However, a simple assessment chart, revised by World Health Organization (WHO) as a part of Integrated Management of Childhood Illness (IMCI) strategy, can be referred for quick assessment of dehydration. WHO classifies dehydration as *no* dehydration, *some* dehydration and *severe* dehydration based on the presence of a few reliable clinical signs (**Table 2**).

MANAGEMENT

Acute watery diarrhea with or without vomiting is a common illness in under-5 children and is mostly caused by self-limiting bacterial or viral infections of GIT. However, it may also be a manifestation of other systemic illnesses. Therefore a careful history and thorough clinical examination to rule out other illnesses is enough to make a diagnosis and there is no need for routine stool examination. A child with diarrhea should be assessed to determine the:

- Nature and pattern of diarrhea
- State of hydration
- Presence of other problems like blood in the stools or severe malnutrition, and
- Screening for concurrent illness like pneumonia, otitis media and meningitis.

An algorithmic approach to assess a sick child up to 5 years of age using IMCI or the Indian adapted version named Integrated Management of Neonatal and Childhood Illness (IMNCI) guidelines is helpful in identifying cases with or without other illnesses and classifying them for management.

Assessment of Dehydration

Presence and severity of dehydration can be assessed with help of IMCI/IMNCI classification tables (Refer to Chapter 51.5 on IMNCI). According to the assessment chart, a patient may be classified as *severe dehydration* (with two or more signs suggestive of severe losses of fluid and electrolytes), *some dehydration* (includes signs of mild and moderate dehydration—identified by the presence of at least two of the signs in this category in the chart) or *no dehydration* (no signs of severe or some dehydration). Depending upon the state of hydration, children with *no dehydration* (Plan A) or *some dehydration* (Plan B) can be successfully treated with ORT and the ones with *severe dehydration* should be initially rehydrated by IV therapy (Plan C) and supplemented by/changed over to rehydration by ORS as soon as the child is able to take orally (**Table 3**).

Physiological Basis for Calculation of Deficit Therapy

Severe dehydration The fluid deficit in severe dehydration is expected to be 10% body weight or more. Therefore the approach is to quickly rehydrate the child with 30 mL/kg body weight for immediate replacement of ECFV followed by 70 mL/kg body weight for correction of remaining fluid deficit. Correction of deficit is spaced over 6 (1+5) hours in infants less than 12 months and 3 ($\frac{1}{2} + 2\frac{1}{2}$) hours in older children. For correcting dehydration due to uncorrected deficit of more than 10% and ongoing losses, hydration is reassessed after 3 hours in older children and 6 hours in infants less than 1 year to decide the next treatment plan. Ringer lactate is the preferred solution for IV rehydration since it provides adequate concentration of sodium and sufficient lactate which is metabolized to bicarbonate for correction of acidosis. Normal saline can be used as an alternative if Ringer lactate is not available. To encourage oral rehydration as soon as possible, the child should be offered ORS (5 mL/kg/h) along with IV infusion as soon as he/she is able to drink orally.

Some dehydration The fluid deficit in some dehydration is expected to be 5–10% of body weight. Therefore an electrolyte solution of appropriate composition (low osmolarity ORS) is administered in the dose of 50–100 mL/kg body weight over 4 hours. Since oral intake of ORS is a good indicator to monitor oral rehydration, children can drink more ORS than the calculated amount depending upon their state of hydration and ongoing losses. After 4 hours, hydration status is reassessed to decide the next treatment plan.

No dehydration The purpose is to replace ongoing losses and to prevent dehydration. Therefore 10 mL/kg body weight of recommended home available fluids/low osmolarity ORS is given for every loose stool. The commonly recommended safe home available fluids include food based fluids, correctly prepared salt and sugar solution, plenty of water along with food and frequent breastfeeding.

Oral Rehydration Therapy

Oral rehydration therapy has radically changed the treatment of diarrheal diseases. The term ORT includes:

- ORS solution of WHO recommended composition,
- Solution made from sugar and salt (if prepared correctly),
- Food based solutions (with appropriate concentration of salt), given along with continued feeding.

The use of ORS to treat diarrhea stems from the discovery during 1960s of the coupled active transport of glucose and sodium in the small bowel resulting in the passive absorption of water and other electrolytes even during copious diarrhea. Results of several studies have shown that optimum absorption of glucose takes place from the intestines between a glucose concentration of 111–165 mmol/L and the sodium:glucose ratio between 1:1 and 1:1.4. Therefore, the standard WHO/UNICEF ORS formula

Table 2 Assessment of dehydration in a child with diarrhea

Treatment plan	Plan A	Plan B	Plan C
<i>Clinical signs</i>			
General condition	Well, alert	Restless, irritable	Lethargic or unconscious
Eyes	Normal	Sunken	Sunken
Thirst	Drinks normally, not thirsty	Drinks eagerly, thirsty	Drinks poorly, not able to drink
Skin pinch	Goes back quickly	Goes back slowly	Goes back very slowly
<i>Decide hydration status</i>	The patient has NO DEHYDRATION	If the patient has two or more signs, there is SOME DEHYDRATION	If the patient has two or more signs, there is SEVERE DEHYDRATION

Table 3 Rehydration therapy for acute diarrhea

Treatment plan	Plan A	Plan B	Plan C
State of hydration	No dehydration	Some dehydration	Severe dehydration
Percentage of body weight loss	< 5	5–10	> 10
Estimated fluid deficit (mL/kg)	< 50	50–100	> 100
Goals of management	Replacement of ongoing losses of fluid and electrolytes	Correction of existing deficits of fluid and electrolytes	Urgent replacement of existing deficits of fluid and electrolytes
Fluid therapy	Maintenance (oral)	Rehydration (oral)	Rehydration (IV)
Treatment facility	Home	Health facility	Health facility
Rehydration fluid	Home available solutions/ORS	ORS	Ringer's lactate*
Amount of rehydrating fluid	For every loose stool: 10 mL/kg body weight or Children < 2 years (50–100 mL) Children 2–10 years (100–200 mL)	50–100 mL/kg body weight (average 75 mL/kg) over 4 hours** plus Older children and adults: Free access to: drinking water in addition to ORS	Intravenous fluids Infants: 30 mL/kg × 1 hour followed by 70 mL/kg × 5 hours Older children and adults: 30 mL/kg × 1/2 hour followed by 70 mL/kg × 2 1/2 hours. plus ORS (5 mL/kg/hour) to be started orally as soon as the child is able to drink
Monitoring	Watch for vomiting for early signs of dehydration, blood in the stools, etc. Reassess after 2 days or earlier	Monitor every hour and reassess after 4 hours: – If still in Plan B, repeat as above – If rehydrated shift to Plan A on ORS	Monitor half hourly and reassess after 6 (infants)/3 hours: – If still in Plan C, repeat as above – If rehydrated shift to Plan B or A as per hydration status

* Normal saline (0.9% NaCl) or half strength Darrow's solution may be used if Ringer's lactate is not available.

** Severely malnourished children should be rehydrated slowly over 6–12 hours.

Abbreviations: ORS, oral rehydration solution; IV, intravenous.

containing sodium chloride 3.5 g, sodium bicarbonate 2.5 g or trisodium citrate 2.9 g, potassium chloride 1.5 g and glucose 20 g to be dissolved in 1 liter of clean drinking water (Na^+ 90 mmol/L, K^+ 20 mmol/L, Cl^- 80 mmol/L, HCO_3^- 30 mmol/L or citrate 10 mmol/L, and glucose 111 mmol/L) was initially introduced for prevention and treatment of dehydration. Standard WHO/UNICEF ORS has been successfully used for decades and it has saved millions of lives. However, low osmolarity ORS is now recommended for prevention and treatment of diarrheal dehydration.

Low Osmolarity ORS

In the past, numerous studies have been undertaken to develop an *improved ORS* which, in addition to known clinical benefits of ORS, would reduce stool output or have additional clinical benefits. Reduction in the osmolarity of ORS has been one of the successful attempts to reach towards this goal. Reduced osmolarity of ORS is achieved by reducing the solution's glucose and salt concentrations which minimizes possible adverse effects of hypertonicity on net fluid absorption. Low osmolarity ORS is safe and efficacious in treating children with acute noncholera diarrhea, and in children and adults with cholera. In the combined analysis of these multicenter studies with ORS osmolarity ranging from 210 mOsm/L to 268 mOsm/L and sodium between 50 mEq/L and 75 mEq/L, there was a reduction in stool output by 20% and reduction in the incidence of vomiting by 30%. Experience of using low osmolarity ORS in children from 1 month to 2 years of age with AD and dehydration in some developing countries has also

suggested that low-sodium, low-glucose ORS formulation reduces the need for IV fluids by 33%. Because of the improved effectiveness of reduced osmolarity ORS solution, especially for children with acute noncholera diarrhea, WHO and UNICEF now recommend that countries use and manufacture low osmolarity ORS (**Table 4**) in place of previously recommended standard ORS solution.

Zinc Supplementation

Zinc deficiency is common in children from developing countries because of intake of predominant vegetarian diets and the high content of dietary phytates. Moreover, increased fecal losses during repeated episodes of diarrhea aggravate pre-existing zinc deficiency. Therefore WHO and Indian Academy of Pediatrics recommends zinc supplementation as an adjunct to ORS in the treatment of diarrhea. All children older than 6 months suffering from diarrhea should receive a uniform dose of 20 mg of elemental zinc as soon as diarrhea starts and continue for a total period of 14 days. Children aged 2–6 months should be advised 10 mg per day of elemental zinc for a total period of 14 days. Zinc not only decreases the stool frequency, and duration of the acute episode, it also prevents future episodes of diarrhea in next 6 months.

Electrolyte and Acid-base Disturbances

Hypertremia Some children with diarrhea, especially young infants, develop hypernatremic dehydration which usually follows use of hypertonic drinks (canned fruit juices, carbonated cold drink, incorrectly prepared salt and sugar solution, ORS with high glucose content). Children with *hypernatremic dehydration*

Table 4 Low osmolality oral rehydration solution (ORS) formulation recommended by WHO/UNICEF

Reduced osmolality ORS	g/liter	Reduced osmolality ORS	mmol/liter
Sodium chloride	2.6	Sodium	75
Glucose, anhydrous	13.5	Chloride	65
Potassium chloride	1.5	Glucose, anhydrous	75
Trisodium citrate, dihydrate	2.9	Potassium	20
		Citrate	10
		Total osmolality	245

(serum sodium > 150 mmol/L, osmolality > 295 mOsm/kg water) are extremely thirsty, out of proportion to their other signs of dehydration and sometimes have convulsions. Patients with hypernatremic dehydration have a total body deficit of sodium, even though the concentration of this cation in serum and ECF is abnormally high. Therefore infants with overt diarrheal dehydration of the hypernatremic variety can be successfully treated with low osmolality ORS. Rapid absorption of this solution during the rehydration phase leads to expansion of intravascular compartment and increases renal perfusion. Administration of plain water provides free water for the infant's renal physiologic mechanism with which to carry out further homeostasis. However, if the child is unable to drink orally, Ringer lactate can be initially given to treat shock and later switch over to ORT with ORS alternating with plain water.

Hyponatremia Patients who ingest only large amount of water or watery drinks that contain very little salt, may present with hyponatremia (serum sodium < 130 mmol/L, osmolality < 275 mOsm/kg water) which may be clinically associated with lethargy and seizures. ORS solution is safe and effective therapy for hyponatremia also. However, in the treatment of hyponatremia, administration of ORS alone without extra water has been observed to be superior because of higher sodium intake. For children who are unable to drink orally, IV infusion of Ringer lactate can effectively treat hyponatremia.

Hypokalemia Inadequate replacement of potassium losses during diarrhea can lead to potassium depletion and hypokalemia (serum potassium < 3 mmol/L) which may result in muscle weakness, paralytic ileus, renal impairment and cardiac arrhythmias. Severe potassium depletion particularly in malnourished children may lead to acute onset flaccid paralysis ranging from neck flop to quadriplegia and respiratory paralysis. The potassium deficit can be corrected by using ORS for rehydration therapy and by feeding potassium rich foods (e.g., banana, fresh fruit juices) during and after diarrhea. Oral potassium supplementation (2 mmol/kg/day) is indicated in malnourished children. In transient flaccid paralysis due to hypokalemia, potassium can be administered parenterally by using 15% solution of potassium chloride (1 mL = 2 mmol of potassium) but not exceeding 4 mmol/kg/day and 40 mmol/L of IV fluids after ensuring adequate renal functions.

Metabolic acidosis During AD, large amount of bicarbonate may be lost in the stool. If the kidneys continue to function normally, most of the lost bicarbonate is replaced and a serious base deficit does not develop. Metabolic acidosis tends to correct spontaneously in most of the cases as the child is properly rehydrated. ORS contains adequate bicarbonate/citrate to counter acidosis in less severe cases. However, in severe dehydration, compromised renal function leads to rapid development of base deficit and metabolic acidosis. Hypovolemic shock as a consequence of rapid loss of water and electrolytes in severe diarrhea results in excessive production of lactic acid which may further contribute to metabolic acidosis. Therefore rapid IV infusion of Ringer's lactate, which

contains 28 mmol/L of lactate to get metabolized to bicarbonate, is recommended in severe dehydration. However, in the presence of circulatory failure bicarbonate precursors may not be readily metabolized in the body.

If the patient presents with severe metabolic acidosis (pH 7.20, serum $\text{HCO}_3^- < 8$ mmol/L), sodium bicarbonate in a bolus dose of 2.5 mmol/kg can be given to correct acidosis. If the facilities for acid base estimation are available accurate dose of bicarbonate can be calculated by the formula: bicarbonate dose (mmol) = desired HCO_3^- – observed $\text{HCO}_3^- \times 0.6 \times$ body weight (kg). It is preferable to increase the bicarbonate level only up to 12 mmol/L to prevent overshoot metabolic alkalosis. Attention should be paid to serum potassium concentration as correction of acidosis in a patient with low potassium can lead to life threatening severe hypokalemia.

Antibiotics

Acute watery diarrhea in under-5 children is mostly caused by self-limiting bacterial or viral infections of GIT. Therefore there is no benefit in prescribing antibiotics as they do not significantly alter the clinical course. On the contrary, they may lead to undesired side effects and consequences. Antibiotic therapy should be reserved for cases of dysentery and suspected cholera only (Chapter 36.2 Dysentery; Chapter 36.3 Cholera). Antibiotics can also be given when the child is severely malnourished or is having coexisting severe systemic infection.

Risk Factors for Diarrheal Morbidity and Mortality

Early home therapy with ORT at the onset of a diarrheal episode remains the treatment of choice in almost all cases of diarrhea. However, it may be necessary to identify on the first day of an episode of diarrhea, signs and symptoms which indicate an increased likelihood of developing dehydration. Alteration in thirst (increased in a normal child and decreased in a dehydrated child as his hydration worsens), six or more loose stools, presence of fever, vomiting and a reduction in appetite are some of the clinical features which can help to recognize potentially severe cases who should be kept under closer surveillance. Associated major infections (pneumonia, septicemia or meningitis), severe wasting and severe stunting have been reported as risk factors for fatal diarrhea and hence such children need to be identified and targeted for intensive intervention.

Nutritional Management during and After Diarrheal Episode

Diarrhea is a major cause of malnutrition owing to low food intake during the illness, reduced nutrient absorption in the intestine, and increased nutrient requirements as a result of the infection. Poor appetite, vomiting and the common practice of withholding or diluting food are some of the reasons for poor intake during an episode of diarrhea. Therefore, food intake should never be restricted during or following diarrhea. Rather, the goal should be to maintain the intake of energy and other nutrients at as high a level as possible. When this is done, even with only 80–95% carbohydrates, 70% of fat and 75% of nitrogen being actually absorbed during acute diarrhea, sufficient nutrients can be absorbed to support continued growth and weight gain. Continued feeding also speeds the recovery of normal intestinal function, including the ability to digest and absorb various nutrients. In contrast, children whose food is restricted or diluted usually lose weight, have diarrhea of longer duration, and recover intestinal function more slowly.

During an episode of diarrhea specific recommendations for feeding are determined by the child's age and feeding pattern before the illness and the state of hydration. If the child is dehydrated, during the rehydration phase breastfeeding should be continued

and normal feeding resumed after rehydration is completed. However, in severely malnourished children some food should also be offered as soon as possible during the rehydration period. *After the rehydration phase* the dietary management during an episode of diarrhea include: (1) breastfeeding should be continued, as often as the child wishes; (2) young infants who take animal milk should continue to take undiluted milk as before; (3) children 6 months of age and older should receive energy rich mixture of soft weaning foods in addition to breastmilk or animal milk; (4) energy rich food (thick preparations of staple food with extra vegetable oil or animal fats), potassium rich foods (legumes, banana), and carotene containing foods (dark green leafy vegetables, red palm oil, carrots, pumpkins) should be given to the child in sufficient quantity. In young children these foods should be particularly well cooked and soft or mashed to aid digestion. Owing to loss of appetite or vomiting, children may need considerable encouragement to eat. It is helpful to give food frequently in small amounts, i.e., six times per day or more.

After an episode of diarrhea, a child should receive more food than usual for at least 2 weeks after diarrhea stops. During this period, the child may consume up to 150 kcal/kg of body weight per day. A practical approach is to give the child at least one extra meal each day with energy rich foods.

DIFFICULT DIARRHEA

Acute watery diarrhea is a common self-limiting disorder in children which can be successfully managed with ORT, zinc supplementation and proper feeding. However, there are clinical situations where extra care needs to be taken while assessing and managing the cases because of a higher risk of complications and mortality. Diarrhea may be difficult to manage in these cases because of younger age, associated systemic infections, poor nutritional status or immune deficiency. Management of these cases may require estimation of serum electrolytes and other investigation to rule out sepsis and associated infections.

Diarrhea in Neonates

Acute watery diarrhea in neonates, especially in breastfed babies, can be a manifestation of systemic sepsis or urinary tract infection. Neonates are at a higher risk of getting dehydrated, assessment of dehydration can be difficult and risk of electrolyte imbalance is higher besides worsening of the clinical condition because of the associated problems. Therefore apart from a thorough clinical examination it may be necessary to estimate serum electrolytes and investigate the neonate to rule out sepsis. In the past several problems like risk of excessive sodium retention, slow correction of acidosis, periorbital edema, mild pedal edema and excessive irritability and higher incidence of hyponatremia have been reported with the use of standard WHO ORS. With the currently recommended low osmolarity ORS these problems have been overcome. Apart from ORS and feeding, antibiotics are also recommended in neonates with low birthweight and associated infections. Continuing and increasing breastfeeds is the best way to keep the baby well hydrated.

Diarrhea in Severely Malnourished Children

Diarrhea in severely malnourished children deserves special attention owing to certain pathophysiological changes in water and electrolyte balance peculiar to protein energy malnutrition (PEM). Children with severe PEM have an increase in total body water and sodium while potassium stores in the body are depleted. The renal concentrating capacity is poor and thus they cannot conserve water efficiently. Moreover, they cannot handle excessive fluid and salt load and can develop fluid retention. Hence,

malnourished children are more prone to diarrheal dehydration, and if given excessive fluids run a risk of developing cardiac failure. This risk is further increased by the fact that it is often difficult to judge the extent of dehydration in these children owing to absence of subcutaneous fat. Assessment of hydration status is also difficult because a number of signs that are normally used are unreliable. Marasmic children normally have sunken eyes, and the diminished skin turgor may be masked by edema in children with kwashiorkor. In both types of patients, irritability or apathy makes assessment of mental state difficult. Signs that remain useful for assessing hydration status in severe PEM include: eagerness to drink (signs of some dehydration); very dry mouth and tongue, cool and moist extremities and weak or absent radial pulse (signs of severe dehydration). It is often difficult to distinguish between some dehydration and severe dehydration in severely malnourished children and it is best to assume at least some dehydration in them if they have acute watery diarrhea.

Several studies have highlighted the need for a separate rehydrating solution for children with PEM because of a higher risk of hypo- or hyponatremia and hypokalemia with the previously used standard WHO/UNICEF ORS. However, the currently recommended low osmolarity ORS is safer in these children. Some key recommendations for managing children with PEM are summarized in **Box 1**.

BOX 1 Treatment of diarrhea in severe malnutrition

- Rehydration, particularly with intravenous fluids should be slow and monitored.
- ORT should be preferred to intravenous fluid therapy because thirst can regulate the amount of oral intake of ORS to prevent under/overhydration.
- Serum electrolyte estimation is helpful to prevent/monitor electrolyte imbalance.
- Perform relevant investigations to rule out septicemia and associated infections.
- Children with PEM should be encouraged to eat even during the oral rehydration phase. Potassium rich food should be offered to the child as soon as child has started eating.
- Apart from low osmolarity ORS, zinc supplementation and feeding, a single mega dose of vitamin A (50,000 IU in infants less than 6 months, 100,000 IU between 6 months and 12 months and 200,000 IU in children > 2 years) should also been given.
- In severe malnutrition, the usual signs of infection such as fever are often absent, yet multiple infections are common in these children. Hypoglycemia and hypothermia are often signs of severe infection. Therefore, all severely malnourished children should be treated with antibiotics. Initiate therapy with broad spectrum parenteral antibiotics like ampicillin or crystalline penicillin with gentamicin.
- Treat micronutrient deficiencies and comorbidities.

Abbreviations: ORT, oral rehydration therapy; PEM, protein energy malnutrition; ORS, oral rehydration solution.

Diarrhea in HIV-infected Children

Diarrhea occurs more commonly in HIV-infected children and these children have a higher risk of mortality in comparison to uninfected children. Cryptosporidium is recognized as a common pathogen to cause diarrhea in these children. These children are likely to have recurrent episodes of acute watery diarrhea as well as persistent diarrhea. Each episode of diarrhea in HIV-infected children is influenced and at times complicated by their immunological status, infection with opportunistic organisms, associated malnutrition and presence of other infections that

increase susceptibility, GI manifestations of primary HIV disease and GI symptoms associated with antiretroviral drugs. Response to oral rehydration may also be unsuccessful in some cases. Therefore apart from standard case management of acute watery diarrhea, these children need to be thoroughly assessed for associated problems and closely monitored for any additional intervention.

Situations when ORT may not be Successful

Some children with *no* or *some* dehydration may require to be given IV fluids with or without ORT in the presence of high rates of purging (watery stools >15 mL/kg/hour), persistent vomiting, (four or more episodes of vomiting/hour) or inability to drink (due to severe stomatitis, fatigue, central nervous system depression induced by antiemetics or antimotility drugs). Glucose malabsorption following intake of ORS is not very common but can cause worsening of diarrhea. In such situations ORS should be withheld and rehydration done with IV fluids.

PREVENTION

Comprehensive diarrhea prevention package includes vaccines, nutritional interventions and improving hygiene and sanitation. Rotavirus accounts for 30–50% of all hospitalizations for acute diarrhea. Improving hygiene and sanitation alone may not prevent rotavirus infection. Natural protection against a subsequent infection with rotavirus has been reported only in 40% children after a single natural infection. Therefore immunization of young children with a rotavirus vaccine is an effective way of preventing at least episodes of severe watery diarrhea in children. Effective vaccines against rotavirus are commercially available. Improving measles vaccine coverage is also expected to have an impact on the prevalence of postmeasles diarrhea.

Promotion of exclusive breastfeeding, zinc and vitamin A supplementation and management of undernutrition are key nutritional interventions for preventing diarrhea in children. Handwashing, safe disposal of stools, preventing water contamination and food-borne transmission, discouraging bottle feeding and fly control are some of the effective measures for improving hygiene and sanitation.

IN A NUTSHELL

1. Acute watery diarrhea is a self-limiting disorder and is successfully managed with ORT, zinc supplementation and continued feeding.
2. Acute watery diarrhea is frequently caused by ETEC, EPEC and rotavirus but antibiotics do not have any beneficial role and therefore not recommended.
3. Oral rehydration therapy is the cornerstone of management of acute watery diarrhea. Intravenous fluid therapy is indicated only in severe dehydration and in the presence of high purge rate, persistent vomiting, inability to drink and glucose malabsorption.
4. Feeding should be started as soon as the child is rehydrated. Feeding should be started during rehydration phase in children with severe malnutrition.
5. Breastfeeding should be continued.
6. Diarrhea in neonates, severe malnutrition and HIV positive children deserves special attention.
7. Handwashing, safe disposal of excreta and maintaining personal and domestic hygiene can help prevent diarrheal episodes.
8. Rotavirus vaccine is an effective intervention to prevent severe episodes of dehydrating diarrhea.

MORE ON THIS TOPIC

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Chapter 36.2

Dysentery

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Dysentery, also called as invasive diarrhea and manifested by blood in the stool, is a major public health problem in less developed countries. The common causes of dysentery in south Asia are shigellosis, amebic dysentery, *Campylobacter spp.*, and *Salmonella spp.* Other viral, bacterial and parasitic agents known to cause dysentery are listed in **Table 1**.

SHIGELLOSIS

The World Health Organization (WHO) estimates that shigellosis accounts for about 140–160 million cases each year. The vast majority of cases occur in developing countries among children aged less than 5 years. About 1.1 million people are estimated to die due to shigellosis globally each year and 60% of deaths are among very young children.

Epidemiology

Since first description of genus *Shigella*, there was a major global shift in the prevalence of four species. Until World War 1 and 2, *Shigella dysenteriae type 1* was predominant isolate which had caused a severe and devastating epidemic that affected Europe, particularly in eastern European countries during the two world wars. It was said that more people died due to shigellosis than the number of people died directly from bullets during these two world wars.

In the recent past there was another pandemic affecting Central America and caused several deaths due to *S. dysenteriae 1*. The epidemic was first noted in Guatemala and quickly spread to other countries such as Panama, Mexico and Costa Rica, caused more than 30,000 deaths within short span of time. During the same time period (1969–1973) another pandemic occurred in South Asia affecting Bangladesh, India and Sri Lanka. This epidemic seems to start in southern part of Bangladesh and then spread to India and Sri Lanka. The causative organism was found to be multidrug resistant *S. dysenteriae 1*.

Table 1 Bacterial, parasitic and viral causes of dysentery

Bacteria:
1. <i>Shigella spp.</i>
2. <i>Salmonella spp.</i>
3. <i>Campylobacter jejuni</i> and <i>Campylobacter coli</i>
4. Enteroinvasive <i>E. coli</i>
5. <i>Yersinia enterocolitica</i>
6. <i>Vibrio parahaemolyticus</i>
7. <i>Aeromonas hydrophila</i>
8. <i>Plesiomonas shigelloides</i>
Parasites:
1. Amebic dysentery (<i>E. histolytica</i>)
2. Bilharzial dysentery (<i>Schistosoma</i>)
3. <i>Balantidium coli</i> and <i>Isospora hominis</i>
4. <i>Strongyloides stercoralis</i>
5. <i>Trichuris trichiura</i>
Viruses:
1. Cytomegalovirus
2. Herpes simplex

Pathogenesis

Shigellae are divided in four groups or species containing 39 serotypes. Group A (*S. dysenteriae*), group B (*S. flexneri*) and group C (*S. boydii*), contains several serotypes, while group D (*S. sonnei*) contains of single serotype.

Mode of Spread

The transmission is through feco-oral route. Shigellae are orally ingested and pass down to stomach. Only few organisms as low as 100 bacteria can cause infection and disease because they can survive in a low pH and can survive the gastric acid barrier. In contrast, a few millions of bacteria are needed to cause diarrhea due to *Escherichia coli* or *Vibrio cholerae*. Most cases of shigellosis result from of person-to-person transmission through contaminated food and water. Transmission rates also correlate with poverty, poor sanitation, personal hygiene, and overcrowding. Only human and higher primates are natural host and reservoir of *Shigella* organisms. In order to produce the disease, *Shigella* organism must possess a smooth lipopolysaccharides (LPS) O antigen, must have genes encoding ability to invade epithelial cells and proliferate therein, and elaborate a cytotoxin for causing cell invasion.

The essential step in pathogenesis is invasion of colonic epithelial cells and parallel cell-to-cell spread of infection. This step involves initial attachment of the organism to the colonic cells followed by entry to the cells by endocytic mechanism. Then the organism invades the adjacent colonic cells. Although, invasion is initially innocuous, subsequently intracellular multiplication occurs, and causes cell damage by inhibiting deoxyribonucleic acid (DNA) synthesis, which ultimately causes cell death resulting in mucosal ulceration. These events are complicated, and require the functions of multiple genes and regulatory elements encoded on both chromosomes. The virulent factor for cellular attachment and penetration are determined by special gene coding.

Shigella has the ability to produce three distinct types of toxins, such as *enterotoxin* that is believed to produce watery diarrhea, *cytotoxin*, that cause dysentery or bloody diarrhea, and a *neurotoxin* which causes neurological manifestations. The enterotoxic property of the organism has been documented in experimental studies with rabbit ileal loops, where injecting shiga toxin produced fluid secretion like enterotoxigenic *Escherichia coli* (ETEC), or cholera toxin. Secretion of shiga toxin is mediated by cyclic-adenosine monophosphate (c-AMP), similar to cholera toxin. The initial phase of watery diarrhea is thought to be due to this mechanism. The cytotoxic ability has been documented by experimental study *Serény test*, where shiga toxin was put to guinea pig eyes that produce keratoconjunctivitis. When Shiga toxin was injected in rabbit, which caused paralyses of limbs and produced convulsions in animal. These might explain association of encephalopathy and convulsions in young children with shigellosis.

Clinical Manifestations

Symptoms

A child with typical shigellosis presents with an acute onset, usually moderate to high fever, malaise, headache, initially watery diarrhea, abdominal pain with cramp, followed by frequent passage of bloody mucoid stools along with straining and tenesmus during defecation. The fever is usually high in young children and sometime associated with convulsions. The initial phase of watery diarrhea usually lasts for 1–2 days, and is followed by bloody diarrhea. Some of shigellosis cases, particularly infected with *S. sonnei*, or *S. boydii* may have a short lasting episode of watery diarrhea and may not proceed to frank bloody diarrhea.

Most cases with *S. dysenteriae type 1* and *S. flexneri* present with bloody mucoid stool. Vomiting is not a major symptom of shigellosis. Severe anorexia and loss of appetite is a major feature of shigellosis in children. Studies have shown several cytokines such as interleukin 1 and 2, alpha-tumor necrosis factor (α -TNF) are involved in producing anorexia. High fever and abdominal pain/discomfort also contribute to anorexia.

Stool frequency is one of the major indicators for identifying shigellosis. Usually mother complains that the child passes more than 10–15 stools per day, and in severe cases the number of stool is as high as 25–30 per day. This is in contrast with amebic dysentery with a usual stool frequency less than 10 per day.

Shigella encephalopathy presents with altered sensorium, vomiting, convulsions, and other upper motor neuron signs.

Clinical Signs

The child is febrile, toxic and irritable. The abdomen is tender usually over the left colon, the affected area of distal colon. Occasionally, a patient may have first degree rectal prolapse, i.e., rectal prolapse during straining and defecation. Third degree rectal prolapse is very uncommon which may be seen in very young children with severe malnutrition. Meningismus may be associated with in *Shigella* encephalopathy.

Complications

Hemolytic-uremic Syndrome

Hemolytic-uremic syndrome (HUS) characterized by microangiopathic anemia, thrombocytopenia, and acute renal failure is primarily a complication occurring in children infected with *S. dysenteriae type 1* and less frequently in patients with *S. flexneri*. The actual pathogenesis is not clear, but it is speculated that shiga endotoxin is involved. Experimental studies suggest that leukocyte mediated intravascular deposition of fibrin occurs in renal vessels.

Seizure

It is one of the neurological complications mostly observed in children and is often associated with high fever. However, some patients may develop convulsions without pyrexia, and Shiga neurotoxin may be involved to cause encephalopathy.

Bacteremia and Sepsis

Bacteremia due to *S. dysenteriae 1* and *S. flexneri* is not uncommon. In about 10% of hospitalized patients with shigellosis, *Shigella* or other gram-negative organism are isolated from blood. Younger age, lack of breastfeeding, and severe malnutrition are associated with a high mortality.

Hyponatremia

Hyponatremia is mostly seen in children infected with *S. dysenteriae 1*. The exact mechanism is not known, however plasma antidiuretic hormone was found to be significantly higher in patients who had hyponatremia, suggesting that syndrome of inappropriate antidiuretic hormone secretion (SIADH) may be responsible.

Malnutrition

Malnutrition as a consequence of shigellosis usually occurs due to several factors such as, loss of appetite, increased catabolism due to high fever, traditional practice of food withholding, and loss of nutrients in the stool. Protein-losing enteropathy is an established mechanism through ulcerated gut. Undernutrition and stunting are the consequences in untreated patient who have a prolonged episode of dysentery causing persistent diarrhea.

Investigations

The white blood cell (WBC) count is usually elevated, but may be normal with shift to left and presence of band cells. Leukemoid reaction (WBC $>50,000/\text{mm}^3$) have been detected in 4% of hospitalized patients with shigellosis in Bangladesh. *S. dysenteriae* was the causative agent in 71% cases and over 70% of patients were children less than 5 years. In complicated HUS, the total WBC count may go up to 60,000–100,000/ mm^3 . Stool microscopy will show plenty of fecal leukocytes, red blood cells and macrophage. Stool culture will grow one of four *Shigella* spp.

Endoscopy of large intestine shows a diffuse colitis, most common in rectosigmoid area, but may extend proximally with longer duration of disease. The intestinal mucosa is erythematous with mucosal edema, friable, and bleeds when touched, and covered with a mucopurulent adherent layer. Histopathological findings from colonic biopsy will show denuded epithelium with microulceration and infiltration of polymorph cells in lamina propria. Crypt abscesses are seen in the mucosa.

Management

Antibiotics

Several clinical studies have shown that appropriate antibiotic therapy reduces the duration and severity of diarrhea, fever, abdominal pain and excretion of pathogens in stool. Choice of antibiotic depends upon the drug sensitivity patterns, availability and the cost. Multidrug resistant *Shigella* infections are common in children and pose a public health challenge. Besides spontaneous chromosomal mutational resistance, transferable drug-resistance mediated by R-Factor is the most important mode of drug resistance in shigellae. Acquisition of an R-Factor simultaneously may confer resistance against several drugs. Therefore information on local sensitivity pattern of *Shigella* isolates can be beneficial while choosing the antibiotics. In view of the fast changing sensitivity pattern, regular monitoring of drug resistance is critical for effective management of shigellosis.

Currently, ciprofloxacin is the drug of choice in most countries, particularly in South Asian countries where shigellosis is prevalent. However, *S. dysenteriae type 1* and *S. flexneri* are becoming increasingly resistant to ciprofloxacin in many countries. Pivmecillinam and ceftriaxone have been found to be effective in those cases. Ciprofloxacin in a dose of 15 mg/kg/dose in a 12 hourly for 5 days is recommended. Oral cefixime is started if there is no response in 48 hours to fluoroquinolone. This treatment is continued for 5 days. For sick children who need hospitalization, injection ceftriaxone is advised (80–100 mg/kg/d \times 5d). Some studies have observed azithromycin to be effective in multidrug resistant shigellosis but recently drug resistance has been reported with azithromycin as well.

Fluid Therapy for Dehydration

Most of the patients have mild to moderate dehydration and oral rehydration with standard oral rehydration solution (ORS) is recommended. However, some young children may have severe watery diarrhea, and may need intravenous (IV) fluid therapy.

Zinc

Administration of zinc, similar to acute watery diarrhea, is recommended for 14 days in all under-5 children with acute dysentery.

Supportive Care

If the patient is febrile and having convulsion, tepid sponging should be done to bring down the temperature. If convulsion is prolonged and recurrent, injection diazepam or phenobarbital

may be required. For managing HUS, whole blood transfusion and early dialysis have been found to have a better outcome. In severe hyponatremia, a slow infusion of a hypertonic NaCl solution (3% NaCl) results in a dramatic improvement in neurological status.

Dietary Management

Shigellosis is usually associated with malnutrition, particularly in young children in developing countries. It is therefore important to maintain calorie intake during acute phase and give additional food during convalescence. Studies done in Bangladesh and elsewhere have shown that a high-energy protein diet for 3 weeks can prevent growth faltering and achieve a rapid catch-up growth.

AMEBIASIS (ALSO SEE SECTION 32 CHAPTER 32.4)

About 10% of world's population is infected with *Entamoeba*, the majority with *Entamoeba dispar*. Amebic dysentery is caused by an intestinal protozoa *Entamoeba histolytica* manifested as prolonged dysentery, a major cause of bloody diarrhea in developing countries. Infection occurs with ingested food containing cyst of *E. histolytica*. Trophozoites of *E. histolytica* invade the gut mucosa. Amebic dysentery has an insidious onset and clinical dysentery usually appears after 2–6 weeks after ingestion of cyst. Patient complains of lower abdominal pain, mild diarrhea that is gradually followed by frank bloody-mucoid stool. The usual stool frequency is 10–12 per day. Stool contains little fecal matter, blood and mucus and have foul smell. Most of the patients will not have high fever like acute shigellosis. Straining and tenesmus are uncommon.

Metronidazole remains as first line of drug for acute intestinal colitis.

CAMPYLOBACTER DYSENTERY

Campylobacter is a gram-negative, motile rod and nonspore forming zoonotic organism and transmitted to humans through animals such as poultry, cattle, and other household animals. *Campylobacter jejuni* and *Campylobacter coli* are major organisms that cause diarrhea and dysentery. In most cases the organism is transmitted through uncooked or raw food products such as meat and milk, and also animal handlings. Although, campylobacter infection occurs in both developed and developing countries, it is highly prevalent and hyperendemic in some areas in South Asia.

Pathogenesis

The organism produces two types of toxins, one *E. coli* heat-labile toxin (LT) like toxin that is responsible for secretory or watery diarrhea, other cytotoxin (CT) that causes bloody diarrhea and dysentery.

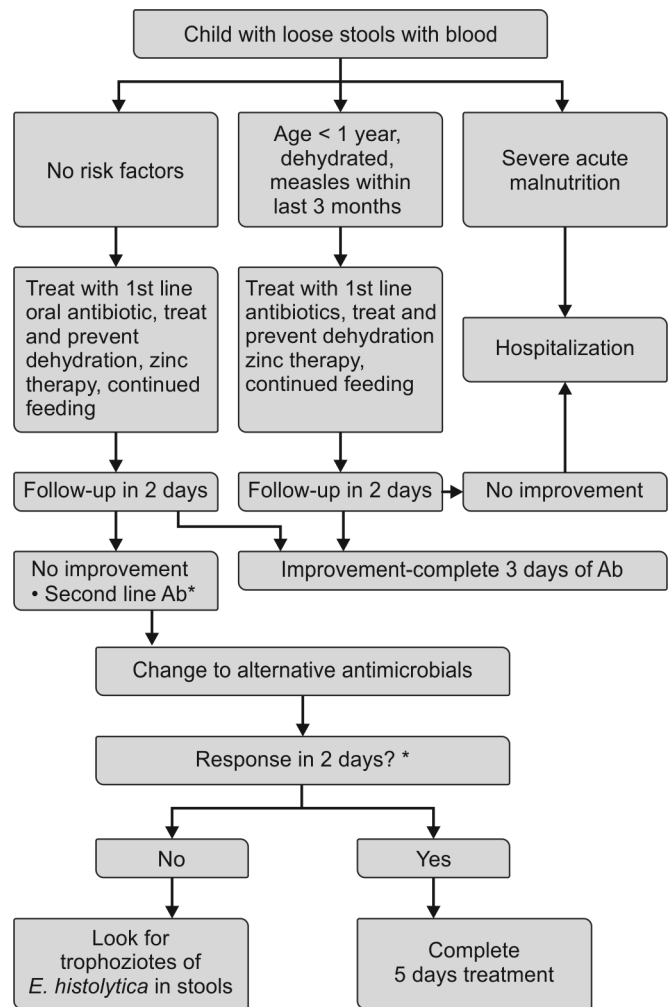
Clinical Features

The clinical presentation is varied, some patients may have profuse watery diarrhea, and some will have severe bloody diarrhea. A typical patient will give a history of fever, nausea, vomiting, initially watery diarrhea followed by bloody mucoid stool. Most patients will complain of abdominal pain with cramps and may mimic acute appendicitis.

Treatment (Flow chart 1)

Diarrhea is usually self-limited, and rehydration with ORS is sufficient in mild to moderate dehydration. Those with severe dehydration require IV fluid therapy. Patients with severe disease with high fever, bloody stool and septic shock require antibiotic therapy. The first line of treatment is erythromycin, given at a dose of 50 mg/kg/day in four divided dosage for 5–7 days. Alternative drugs are clarithromycin, azithromycin and ciprofloxacin.

Flow chart 1 Treatment algorithm of dysentery. Ciprofloxacin and cefixime are the recommended first-line and second-line antibiotics for dysentery, respectively



*Not better in 2 days with first line antibiotic

ENTEROINVASIVE AND ENTEROHEMORRHAGIC E. COLI DYSENTERY

Most *E. coli* [ETEC and enteropathogenic *E. coli* (EPEC)] cause watery diarrhea. However, Enteroinvasive *E. coli* (EIEC) and Enterohemorrhagic *E. coli* (EHEC) cause invasive diarrhea and severe dysentery with bloody stool. The most common serotype is O157:H7 which causes severe dysentery with bloody diarrhea and associated with some life-threatening complications like HUS. It is prevalent in Northern America and some of European countries and usually been associated with outbreaks. Very few cases are reported from South Asia. EIEC and EHEC produce a CT which is like *Shigella* toxin and is named as Shiga-like toxin (SLT) or verotoxin (VTEC). The clinical features include high fever, abdominal pain and frequent passage of bloody stool. Some patients may present with HUS as a complication. Third generation cephalosporins are the treatment of choice.

DYSENTERY DUE TO OTHER CAUSES

Beside these organisms that cause dysentery in majority of cases, other organisms such as *Aeromonas hydrophila*, *Plesiomonas shigelloides*, and *Vibrio parahaemolyticus* have been implicated

to cause dysentery. Anaerobic Gram negative bacteria such as *Clostridium difficile* and *Clostridium perfringens* are two major organisms to produce severe colitis and bloody diarrhea. Any antibiotic that is used for longer duration have been found to be associated with pseudomembranous colitis, details are discussed in a separate chapter on antibiotic associated diarrhea.

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IN A NUTSHELL

1. Dysentery is a major public health problem in less developed countries resulting in serious consequences of wasting and stunting.
2. The common causes of dysentery in south Asia are shigellosis, amebic dysentery, *Campylobacter spp.*, and *Salmonella spp.*
3. More than a million people are believed to die due to shigellosis globally each year and 60% of these deaths are among very young children.
4. *Shigella* group of organisms can survive in a low pH and pass through gastric acid barrier, and therefore only few ingested organisms can cause infection and disease.
5. Multidrug resistant *Shigella* infections are common in children. Therefore knowledge of local sensitivity pattern and regular monitoring of drug resistance is critical for effective management of shigellosis.
6. Ciprofloxacin is the drug of choice for dysentery, non-responders are given cefixime. Serious hospitalized patients are treated with ceftriaxone. Zinc is coadministered in all cases for 14 days. Nutritional support during and after an episode of dysentery is important to prevent malnutrition.
7. Apart from shigellosis, amebiasis and gut infection with *Campylobacter spp.*, Enteroinvasive *E. coli* (EIEC) and Enterohemorrhagic *E. coli* (EHEC) cause invasive diarrhea and severe dysentery

Chapter 36.3

Cholera

Piyush Gupta, Rashi Singhal

Cholera is a toxin mediated acute diarrheal disease caused by contamination of food or water by certain strains of *Vibrio cholerae*. It accounts for approximately 3–5 million cases and 1–1.2 million deaths each year worldwide. Short incubation period and virulence of certain strains like O1 and O139 is responsible for the high fatality.

EPIDEMIOLOGY

In 1883, Robert Koch proved that cholera occurs due to the bacteria *Vibrio cholerae*. However, it was Petten, Kofer and Emmerish, who publicly drank a culture of *V. cholerae* and suffered from the disease, proving beyond doubt the etiological association of *V. cholerae* with cholera. Six pandemics of cholera were reported between 1817 and 1923. Most of these originated from the Gangetic basin of India and Bangladesh. The seventh pandemic (origin: Indonesia, 1961) is currently continuing. It differed from the previous pandemics in two aspects: (1) it was caused by a new organism El Tor *Vibrio*; and (2) it was associated with a low mortality rate, mainly due to advent of oral rehydration solution (ORS) therapy. A new strain of cholera, named O139 emerged in India in 1992. It spread west to Pakistan and east to China, and in the early months of 1993 caused an estimated 100,000 cases and 1,000 deaths in Bangladesh.

Only O1 and O139 strains of cholera result in epidemics. Cholera was reported to be endemic in 80 countries in 1993, affecting millions. But there has been a steady decline in the incidence since then and the number of countries reporting cholera declined to only 48 in 2012 (**Fig. 1**). Africa and Asia account for 96% and 3%

of the global total cases of cholera, respectively. Case fatality rate is now reported as 1.2% as compared to 3.6% in 2000.

MODE OF SPREAD

Cholera is spread through water contaminated with fecal matter. This is mainly related to inadequate facilities for disposal of sewage and provision of portable drinking water. Direct spread by contact does not occur, though the infection may be spread from person to person by contaminated hands and fomites. In developed countries, consumption of raw shellfish or moist grains has been observed to be associated with the disease spread.

PREDISPOSING FACTORS

Cholera is predominantly a disease of young children. Under-5 carry a 10 times higher attack rate as compared to adolescents and adults. In the presence of normal gastric pH, a large inoculum (10^8 – 10^{10} organisms) is needed to overcome the protective barrier and cause disease. Reduced gastric acidity or achlorhydria provides a suitable environment for growth of *V. cholerae* and as low as 10^4 – 10^6 inoculum is sufficient to cause the disease. Blood group O, malnutrition and immunocompromised state are also associated with increased risk for the disease.

Cholera occurs more in tropical countries across the globe and more during warm months. Other environmental factors like poverty, overcrowding, and lack of adequate sanitation and safe drinking water also play a role. In a country like India where nearly two-thirds of the population live in rural areas and only 28% of households use piped drinking water and 26% of households have access to good sanitation, it is not surprising that cholera is endemic. During human congregation, such as festivals, fairs (e.g., *kumbh melas*), following natural calamities (floods, earthquakes) and because of migration of rural population to urban areas, epidemics of cholera are frequent due to overstretching of the normal sanitary arrangements.

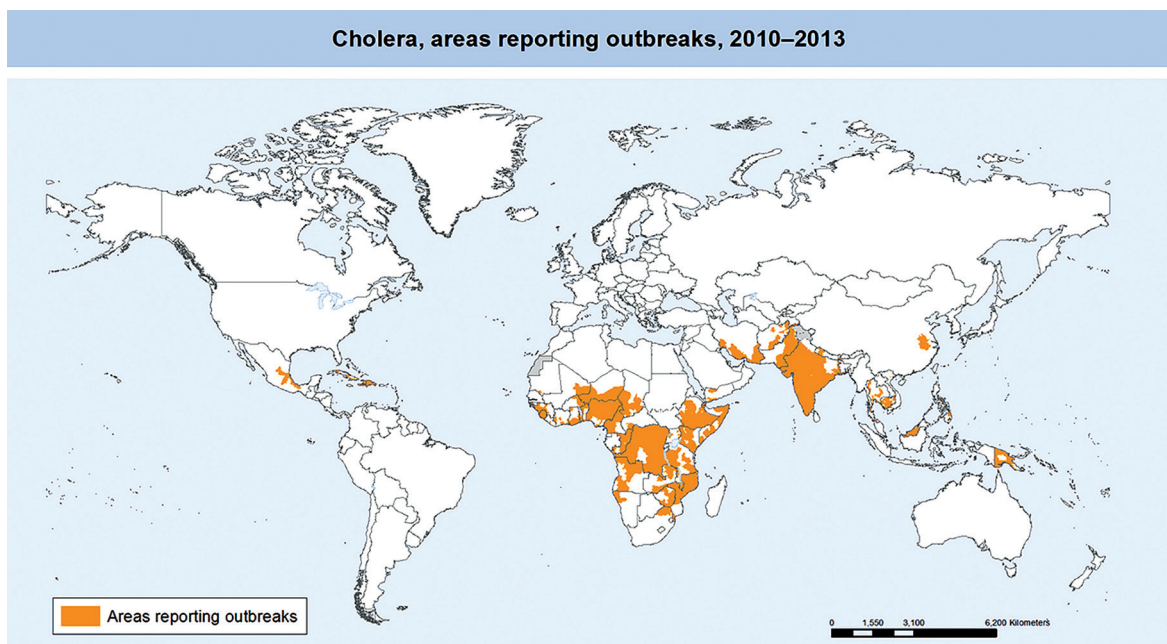
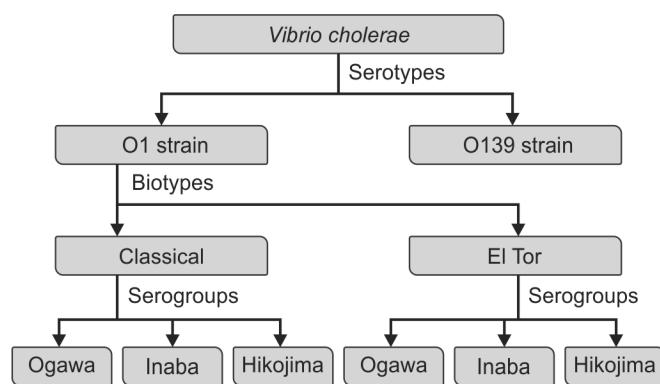


Figure 1 Countries reporting cholera in 2011–12

Source: Reproduced with Permission, WHO.

Flow chart 1 Serotypes, biotypes and serogroups of *Vibrio cholerae*

MICROBIOLOGY

Vibrio cholerae, the causative organism, is a gram-negative, rod shaped curved, motile bacillus. They are fresh, brackish, or saltwater dwelling anaerobes with fermentative metabolism. Vibrios are highly halophilic, heterophilic motile organisms that travel with a single flagellum, and depend on saccharose sugar and starch for their growth and development.

V. cholerae possesses both somatic O and flagellar H antigens. Serological differentiation is based on polysaccharide somatic O antigen. There are over 200 serogroups of *V. cholerae*, but only two serogroups (O1 and O139) are associated with outbreaks of severe disease in man. Other strains may cause mild diarrhea in a sporadic manner. O1 has two biotypes, classical and El Tor; each biotype is further classified into three serotypes based on presence or absence of three antigenic determinants (A, B, C) on the O antigen. These are Ogawa (A and B), Inaba (A and C) and Hikojima (A, B and C) strains (**Flow chart 1**). Among the strains, *V. cholerae* O139, isolated in the Bay of Bengal in 1992, is confined to Southeast Asia.

ETIOPATHOGENESIS

Vibrio cholerae generates several toxins that are responsible for the disease. The major toxin is the cholera enterotoxin called cholera toxin (CT). The *ctxAB* gene encoding the CT is mapped on the genome of a lysogenic filamentous bacteriophage, called *CTXphi*. Horizontal transmission of the genome by bacteriophage might be responsible for the emergence of new strains like O139. CT has 2 subunits—(1) subunit A and (2) subunit B. The A subunit is cleaved to produce A1 and A2 fragments, of which A1 fragment is the active enzyme while the A2 subunit attaches A1 to the B subunit. The B subunit is a pentamer that binds the toxin to the enterocyte surface receptor, the ganglioside GM1. Following binding and internalization of the toxin, A1 catalyzes the ADP-ribosylation of a GTP-binding protein, leading to persistent activation of adenylate cyclase. This results in increased cyclic adenosine monophosphate (cAMP) in the intestinal mucosa that causes increased chloride secretion and decreased sodium absorption, producing the massive fluid and electrolyte loss characteristic of cholera. CT may also lead to increased prostaglandin production, which adds to gastrointestinal loss of water and electrolytes. The cholera enterotoxin (CT) is similar in structure and function to the *Escherichia coli* enterotoxin (LT).

V. cholerae also produces other toxins like neuraminidase, disulfide isomerase, hemagglutinin protease, hemolysin-cytolysin and thermostable direct hemolysin (TDH). All these toxins help in increasing the binding ability of the bacteria and potentiating

CT toxin. Researchers have also postulated the activation of certain other chloride channels like cystic fibrosis transmembrane regulator (CFTR) and calcium activated chloride channels (CaCC) which are activated during infection. Further research is required to explore their exact role in pathogenesis as well as possibility of selective channel blockers for treating cholera.

Intestinal Colonization

Following entry into the gut through contaminated food, the vibrio colonizes the small intestinal epithelium. *V. cholerae* produces a pilus called the toxin-coregulated pilus (TCP), which is absolutely required for colonization of the small intestine. This is encoded by the *tcpA* gene but the expression of gene varies with the biotype. Hemagglutinins act as adhesion factors. They do not have a major effect on virulence but help in activating cholera toxin by nicking the A subunit. Accessory colonization factor and porin-like proteins are the other factors playing a role in colonization.

CLINICAL FEATURES

The incubation period of *V. cholerae* is very short, ranging from 2 hours to 5 days. Man is the only natural host, but free living *V. cholerae* have been recognized in aquatic environment. A case is infectious as long as the person continues to excrete the bacilli. Usually the disease is communicable for 3 days before the onset of symptoms (incubatory carrier period) and 7–10 days thereafter. The ratio of severe cases to subclinical cases is around 1:10. These subclinical cases continue to harbor the bacteria in their feces for 7–14 days after infection and shed back the virus into the environment, potentially infecting other people. Asymptomatic cases serve to maintain the infection in the community. Most of the carriers are temporary, though chronic gallbladder carriage has also been reported up to as late as 11 years (Cholera Dolores). Temporary convalescent carriers may continue to excrete *V. cholerae* for 3–4 weeks.

Most patients (75%) infected with toxigenic *V. cholerae* serogroup O1 or O139 are asymptomatic. Only 20% have only a mild to moderate diarrheal illness and approximately 5% develop the classic symptoms and signs of severe cholera (*cholera gravis*). Diarrhea is usually abrupt, painless and profuse. The stools are voluminous (10–20 mL/kg up to 1 liter per stool), isotonic, and rice watery, with flecks of suspended mucus. This is associated with profound vomiting of clear watery fluid. If fluid losses are not corrected rapidly, patient develops features of severe dehydration and lapses into hypovolemic shock. The child becomes apathetic and lethargic that progresses rapidly to obtundation, hypotension, renal failure and shock. Loss of bicarbonate in stool and lactic acidosis from poor perfusion may result in Kussmaul breathing. Muscle cramping and weakness are common due to loss of potassium and calcium.

Renal failure with acute tubular necrosis may occur as urine output decreases. In children, depletion of glycogen stores and inadequate gluconeogenesis can lead to symptoms of severe hypoglycemia or even coma. The natural course runs for 2–7 days. The purge rate is usually very high (10–20 mL/kg/h up to 1,000 mL/h) and if untreated proves fatal. Death may be attributed to hyponatremic shock, acidosis, and renal failure.

COMPLICATIONS

Rare complications include aspiration pneumonia and septicemia. An unusual and rare presentation of the disease is *Cholera sicca* in which fluid accumulates in the intestinal lumen leading to circulatory collapse and death characteristically in the absence of diarrhea.

DIAGNOSIS

Case Definitions

While management of patients with acute watery diarrhea is similar regardless of the illness, it is important to identify cholera because of the potential for a widespread outbreak. According to WHO, cholera should be suspected if:

- A patient older than 5 years develops severe dehydration from acute watery diarrhea (usually with vomiting); or
- Any child above the age of 2 years has acute watery diarrhea in an area where there is an outbreak of cholera, especially patients who pass the *rice watery* stool typical of cholera.

A case of cholera is confirmed when: *Vibrio cholerae* O1 or O139 is isolated from any patient with diarrhea. Whenever such cases are suspected and confirmed, reporting to health officials becomes mandatory.

Routine Investigations

There is a rise in hematocrit, increase in serum specific gravity and elevation of serum total proteins due to hemoconcentration. There is leukocytosis without left shift, hyponatremia (serum sodium < 135 mEq/L), deranged renal function tests and metabolic acidosis due to enormous intravascular volume loss. Initially potassium remains normal due to exchange with hydrogen ions at the distal tubules but later hypokalemia (serum potassium < 3.5 mEq/L) develops, causing paralytic ileus, muscle weakness, and neck flop.

Stool Examination

Bedside diagnosis rests on the presence of rice water stools coupled with demonstration of darting motility in wet mounts of the stools (*hanging drop preparation*) identified under a dark field microscope at 400X magnification. Isolation and identification of *V. cholerae* serogroup O1 or O139 by culture of a stool specimen remains the gold standard for the laboratory diagnosis of cholera. Identification as well as isolation of the organism is done using selective thiosulfate-citrate-bile salts agar (TCBS) medium. Cary Blair media is used for transport.

Commercially available rapid test kits are available (Crystal VC® immunochromatographic dipstick test for *V. cholerae* O1 and O139, Span Diagnostics Limited, India) to identify an epidemic outbreak especially in resource poor settings. The dipstick is dipped into a stool sample. If two red lines appear on the dipstick, then the patient has cholera. The test takes between 2 minutes and 15 minutes. It is more sensitive (93–98%) than specific (67–96%) which makes it less useful for individual case management in an endemic country like India. However, in the setting of an outbreak of acute watery diarrhea, in which the epidemiological and clinical evidence suggest that 10 or more persons are suffering from the same illness, the overall sensitivity and specificity of the test for the diagnosis of an outbreak of cholera improve. If the cause of the outbreak is cholera, most (an estimated 8–9) of the rapid test results from the 10 individual patients will be positive; if the outbreak is the result of another cause, most of the rapid test results (an estimated 6–7) will be negative. The difference (≥ 8 positive tests vs. ≤ 4 positive tests) should be sufficient to provide a clear indication of whether or not the outbreak of acute watery diarrhea is due to cholera. The test does not provide any information regarding antimicrobial susceptibility testing and subtypes responsible for the outbreak.

Differential Diagnosis

All causes of acute watery diarrhea including rotavirus, *Cryptosporidium* and enterotoxigenic *E. coli* (ETEC) can present with similar manifestations. Presence of rice watery stools in the

setting of an outbreak, high purge rate and rapid and profound fluid loss helps in establishing the diagnosis of cholera.

TREATMENT

Management of Dehydration and Electrolyte Imbalance

Rehydration is the mainstay of therapy. Rehydration therapy reduces the risk of mortality from 10% to 0.5%. Patients are treated as per WHO guidelines for acute watery diarrhea. WHO ORS standard sachets are the mainstay of rehydration therapy. Patients with no dehydration are given home management (Plan A); for those with some dehydration, ORS therapy under supervision is allowed (Plan B). Intravenous (IV) fluid administration (Plan C) is reserved for severely dehydrated patients. For details please see Chapter 36.1 on Acute Watery Diarrhea.

Children with cholera are at a great risk for hyponatremic dehydration and the appropriate choice of fluid used for rehydration is crucial. Usually 0.45% normal saline with 5% dextrose with maintenance potassium or Ringers lactate is preferred for fluid correction once initial boluses have been administered for features of hypovolemic shock as it contains both potassium and bicarbonate which are equally lost in stools. Special solutions like *Dhaka Solution* in endemic areas and *Hartmann Solution* can also be used if available for IV rehydration therapy. Fluid replacement in cholera reaches up to 200–350 mL/kg over the first 24 hours. WHO advocates the use of low osmolarity ORS sachets to be equally effective as the standard ORS sachets for rehydration therapy. However, the chances for biochemical hyponatremia with low sodium ORS sachets are more than the standard ORS sachets even though patient remains asymptomatic (Murphy et al. 2009). Rice based ORS is also proven to be equally efficacious to the standard ORS for rehydration in cholera.

Antimicrobial Treatment

Appropriate antibiotics are essential in the management of cholera as they decrease the duration of diarrhea, reduce the volume of rehydration fluids needed by almost 50%, and shorten the duration of *V. cholerae* excretion to 1–2 days. Options include tetracyclines, fluoroquinolones and macrolides. Among tetracyclines, single dose of doxycycline is equally effective as a 3 day course of tetracycline in terms of stool output, duration of diarrhea, vomiting, and requirement for rehydration therapy. Single dose of ciprofloxacin has proven to be more effective than doxycycline. However, the increasing resistance among the strains of *V. cholerae* against ciprofloxacin in Asia and Africa has restricted its use. Macrolides offer a good alternative in children where tetracyclines are contraindicated. Azithromycin (single dose) and erythromycin have proven to be equally efficacious in terms of clinical and bacteriological cure with rare occurrence of resistance and shown to be better than fluoroquinolones. Cotrimoxazole and furazolidone are rarely used as most *V. cholerae* O139 strains and many O1 El Tor strains are resistant to them. Drug treatment of cholera is summarized in **Box 1**.

BOX 1 Antimicrobials for treating cholera

Antimicrobial	Dose
Doxycycline	4 mg/kg single dose < 15 years, 200 mg stat > 15 years
Tetracycline	12.5 mg/kg/dose 4 times/day for 3 days
Ciprofloxacin	20 mg/kg single dose
Erythromycin	12.5 mg/kg/dose 4 times/day for 3 days
Azithromycin	20 mg/kg single dose
Furazolidone	12.5 mg/kg/dose 4 times/day for 3 days

Zinc Supplementation

Oral zinc supplements (10 mg/day for children less than 6 months and 20 mg/day for those between 6 months and 5 years) for 14 days shortens the duration of illness, decreases the stool volume, decreases the purge rate, and reduces further episodes as in other watery diarrhea. It also has a direct inhibitory action on the CT toxin. However, role of zinc in children older than 5 years with cholera is yet to be proven.

PREVENTION AND CONTROL

Prevention is based on ensuring a safe water supply and adequate facilities for sanitation. In urban areas, properly treated drinking water should be made available through piped supply. The minimum level of free residual chlorine in a piped system should be at least 0.5 mg/L. In rural areas, water can be made potable by boiling or adding a chlorine releasing chemical.

Appropriate facilities for disposal of human waste and excreta should be constructed with the help of the community. Education regarding the use of existing toilet facilities and importance of washing hands must be given utmost importance. In the event of large fairs, festivals, etc., special care should be taken for safe waste disposal.

Community at risk of developing an outbreak of cholera should be educated with regard to importance of healthy feeding practices. Mass chemoprophylaxis, vaccination, and travel restrictions are ineffective in controlling an outbreak. Selective chemoprophylaxis may be useful for members of a particular family who are sharing food with a cholera patient.

Cholera Vaccines

Two types of oral cholera vaccines are available which have proved to be safe, immunogenic and effective: (1) killed oral vaccines (Dukoral, Shanchol) and (2) live oral vaccine (CVD 103-HgR). Parenteral vaccines are withdrawn due to low efficacy (50%), no herd immunity and failure to prevent development of carrier state.

Dukoral (Whole Cell with Recombinant B Subunit)

Dukoral is a monovalent vaccine based on formalin and heat-killed whole cells (WC) of *V. cholerae* O1 (classical and El Tor, Inaba and Ogawa) plus recombinant cholera toxin B subunit. The vaccine has a shelf life of 3 years at 2–8°C and remains stable for 1 month at 37°C. Available in a 3 mL single dose vial, it is essential to be given with a bicarbonate buffer in a glass of water as B subunit is sensitive to stomach acid. Two doses, given 1–2 weeks apart, confer 80–90% protection for 6 months about 7 days after the last dose. Children aged 2–5 years should receive three doses more than 7 days apart (but < 6 weeks apart). One booster dose is recommended by the manufacturer every 6 months for children aged 2–5 years and every 2 years for adults and children aged more than or equal to 6 years in endemic areas. If the interval between primary immunization and the booster is more than 6 months for less than 5 years and more than 2 years for more than 5 years, primary immunization must be repeated. Dukoral is not licensed for children aged less than 2 years. It also offers some cross protection against ETEC strains for around 3 months, being structurally similar to CT toxin. It is not recommended in India currently due to absence of protection against O139 strain, cost and requirement of safe drinking water for its administration.

Bivalent Whole Cell Vaccines

The closely related bivalent oral cholera vaccines Shanchol and mORCVAX based on serogroups O1 and O139 are variants of

the WC/rBS vaccine containing no recombinant B-subunit and have been manufactured in Vietnam and later reformulated to meet WHO standards. Shanchol is currently recommended for use in India as it is safe, immunogenic (80% antibody response in 6 months), cost-effective and does not require a buffer or water for administration. It is also administered in two doses 15 days apart and safe above 1 year of age. Booster dose is recommended after 2 years. This vaccine has no cross protection for ETEC.

CVD 103-HgR Oral Cholera Vaccine

It is a single dose live attenuated vaccine against the O1 strain of *V. cholerae* requiring cold chain and buffer. However, the protective efficacy is less (60%) and does not protect against the O139 strain. It is mainly indicated in travelers to a developing country as it shows protection within 8 days of vaccination.

Certain other oral vaccines like Peru 15, CVD 110, 111 and 112 and Cuban 638 as well as conjugated vaccines are under trials. In 2011, the 64th World Health Assembly recognized the re-emergence of cholera as a significant public health burden and called for the implementation of an integrated and comprehensive approach to cholera control. In 2012, a technical working group initiated a coordinated global cholera management initiative by recommending the creation of a global oral cholera vaccine (OCV) stockpile for use in emergencies.

IN A NUTSHELL

1. Cholera epidemics are caused by *Vibrio cholerae* strains O1 and O139.
2. Pathogenicity is toxin mediated (cholera toxin).
3. Carrier rate is high which may last up to months to years.
4. Diarrhea is usually very severe with a very high purge rate up to 10–20 mL/kg/h.
5. Hanging drop method is a useful bedside test. Dipstick methods are also available. Stool culture is required for confirmation.
6. WHO ORS with zinc is the mainstay of therapy. Single dose of doxycycline, azithromycin or ciprofloxacin provide a good antibiotic cover.
7. Cholera vaccines offer a moderate protection benefit for 1–2 years and booster doses are required in endemic areas.
8. Mass education of adequate sanitation and provision of safe drinking water can help prevent the disease.

MORE ON THIS TOPIC

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Chapter 36.4

Persistent Diarrhea

Shinjini Bhatnagar, Aashima Dabas, Dheeraj Shah

Persistent diarrhea (PD) is defined by World Health Organization (WHO) as diarrhea of a presumed infectious etiology that continues for at least 14 days. Almost three decades back, it was reported to contribute to almost 40% of all under-5 diarrheal deaths. A recently completed review of verbal autopsy data from seven countries surveillance sites (Bangladesh, Ethiopia, Ghana, India, Pakistan, Tanzania and Uganda) found that PD continues to play a major role in infant and childhood diarrheal deaths, especially in high burden countries. Interestingly, in this study, PD contributed to 10–61% of the overall diarrheal deaths, and accounted for more than one-third of all the diarrheal deaths in four countries (India, Pakistan, Tanzania and Ethiopia). Given the overall reduction in childhood mortality from acute diarrhea, the concern is that a major proportion of childhood diarrheal deaths maybe happening in children with PD.

DEFINITION OF PERSISTENT DIARRHEA

The duration of acute diarrhea forms a continuum, most episodes terminate within 7 days and progressively smaller proportions persist beyond 14, 21 or 28 days. WHO defines PD as a diarrheal episode that lasts for 14 or more days. This definition excludes specific conditions like celiac disease, tropical sprue, or other congenital, biochemical or metabolic disorders. The 14-day cutoff for defining PD is arbitrary but is supported by observation of a significant high case fatality rate when diarrhea extends for 2 or more weeks. A significant proportion of children with persistent episode of diarrhea develop malnutrition. These patients require careful assessment and management to reduce mortality.

EPIDEMIOLOGY

Persistent diarrhea continues to play a major role in infant and childhood diarrheal deaths, especially in high burden countries. Community-based studies have estimated that 2–6% of total diarrheal episodes become persistent. The prevalence of persistent episodes is much more common in hospitalized patients because of the referral bias and its association with severe malnutrition and systemic infections. Overall, a greater incidence of PD is reported from developing countries where accessibility to safe water, sanitation and hygiene is limited. The incidence of PD has possibly shown a decline worldwide in the last few decades, which may be attributed to improved management practices of acute diarrhea.

A clear trend towards persistence of a diarrheal episode is noted among infants. Healthy infant feeding practices like exclusive breastfeeding and adequate and timely complementary feeding provide protection against PD. Malnutrition, quantified as wasting, underweight or stunting increases the chances of prolongation of a diarrheal episode into PD. Unnecessary use of antimicrobials in acute diarrhea, vitamin A and/or zinc deficiency, and recent history of measles or HIV infection increase the risk of PD. In addition to the above, various sociodemographic factors such as absence of safe and potable water supply or storage facilities, lack of sanitary latrine, overcrowding and low maternal education have been identified as potential risk factors. Studies have shown that severity of acute diarrhea, as assessed by frequency or presence of dehydration, does not correlate with duration of diarrhea. Likewise, concurrent presence of fever or abdominal pain or vomiting is not a good predictor for PD.

ETIOLOGY

Etiology of PD is multifactorial. Persistent infection with same pathogen, sequential infection and secondary lactose intolerance are the most common reasons. The organisms which are more commonly isolated from children with PD in comparison to acute diarrhea are: Enteroaggregative *E. coli*, *Cryptosporidium spp.* and *Giardia spp.* Both *Cryptosporidium spp.* and *Giardia spp.* are water-borne infectious agents and show clustering in areas with suboptimal sanitation. Giardial trophozoites are motile and can undergo antigenic variations to evade the host immune system. The trophozoite attaches to the jejunum through its ventral disk to result in damage to the microvilli of intestinal lumen and in brush-border enzyme deficiencies, which leads to persistence of a diarrheal episode. Similarly, *Cryptosporidium* also invades the jejunal luminal lining and induces cell apoptosis leading to accelerated loss of villus enterocytes. This manifests as malabsorption and diarrhea. Few other organisms which have also been isolated in PD include non-typhoid *Salmonella*, *Campylobacter spp.* diffusely adherent *E. coli* and *Shigella spp.* Enteroaggregative *E. coli*, *Shigella* and *Cryptosporidium* have been associated with persistent infection while sequential infections are found with multiple pathogens with no clear pattern. The microbes which are less commonly isolated in PD in comparison to acute diarrhea are: Rotavirus, Enterotoxigenic *E. coli*, *Vibrio spp.* and the helminths.

Systemic infections like urinary tract infections, pneumonia and systemic sepsis are also identified in significant proportion of children with PD, especially if they are severely malnourished.

CLINICAL PRESENTATION

Majority of patients with PD pass several loose stools daily but remain well hydrated. Dehydration develops only in some patients because of the high stool output or when oral intake is reduced due to associated systemic infection. The major consequences are growth faltering, worsening of malnutrition and death during a subsequent diarrheal or non-diarrheal illness. The growth failure associated with PD also occurs due to inadequate energy intake during the diarrheal episode. This results from anorexia associated with the illness, faulty feeding practices and incorrect advice by physicians.

Most of the PD patients can be treated at home but infants younger than 6 months particularly those not breastfed, with dehydration or systemic infection or those with severe malnutrition (weight-for-length < 70% or mid-upper arm circumference < 11.5 cm or visible severe wasting or symmetrical pedal edema) are at high risk for complications and may require to be treated in hospitals. All children with PD should be carefully screened clinically for indicators for systemic infection and all those who have severe malnutrition should be assumed to have systemic infection.

MANAGEMENT OF PERSISTENT DIARRHEA

Prevention and Treatment of Dehydration

The child should be assessed for signs of dehydration and treated according to the WHO Treatment Plan A, B or C, as appropriate (as described in Chapter 36.1).

Antimicrobial Therapy

Controlled trials of empirical treatment with large doses of oral gentamicin hypothesized to act locally against the enteric pathogens and the increased small bowel bacterial overgrowth, or sulfamethoxazole-trimethoprim, and combinations of metronidazole with nalidixic acid postulated to act locally on

the enteric pathogen and any associated systemic infection did not show any therapeutic benefits. Although these studies were conducted as far back as the late 1980s and early 1990s and had small sample sizes making their effect estimates imprecise, these or other antimicrobials have not been evaluated in larger trials. Currently, antimicrobial therapy in PD is indicated only in the presence of gross blood in stools or for specific enteric pathogens against which such therapy is known to be beneficial, e.g., *Shigella*, when there is associated systemic infection, or documented urinary tract infection and in those who are severely malnourished.

Additional Drugs

Antimotility and antisecretory agents and bile salt binding resins have not been shown to give any significant clinical benefit when used to treat PD. Larger better quality trials are required to evaluate the new broad spectrum antimicrobials in children with persistent diarrhea; assessing effects on both the clinical and the nutritional outcomes. This would be particularly important in cases where specific pathogens like *Cryptosporidium* and other newer protozoal agents are identified.

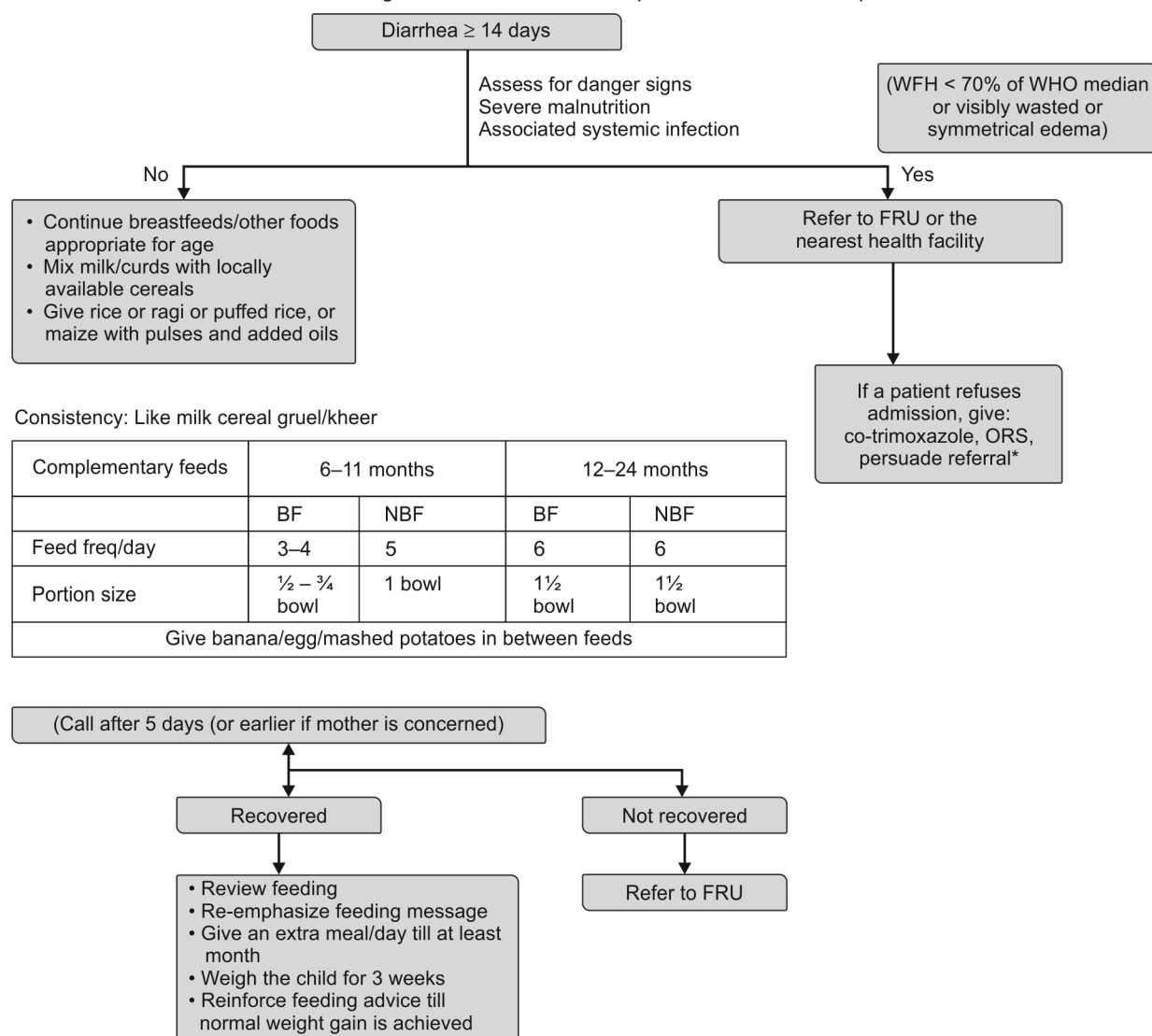
Dietary Management in Older Infants and Young Children

Nutritional therapy is the cornerstone of management of PD. Breastfeeding should be continued as breastfed infants continue to gain some weight even while passing abnormal stools for a few extra days after an acute episode of gastroenteritis. In the second and later years, breastmilk output is less and optional feeding of a mixed diet is more important.

Dietary Algorithm (Flow charts 1 and 2)

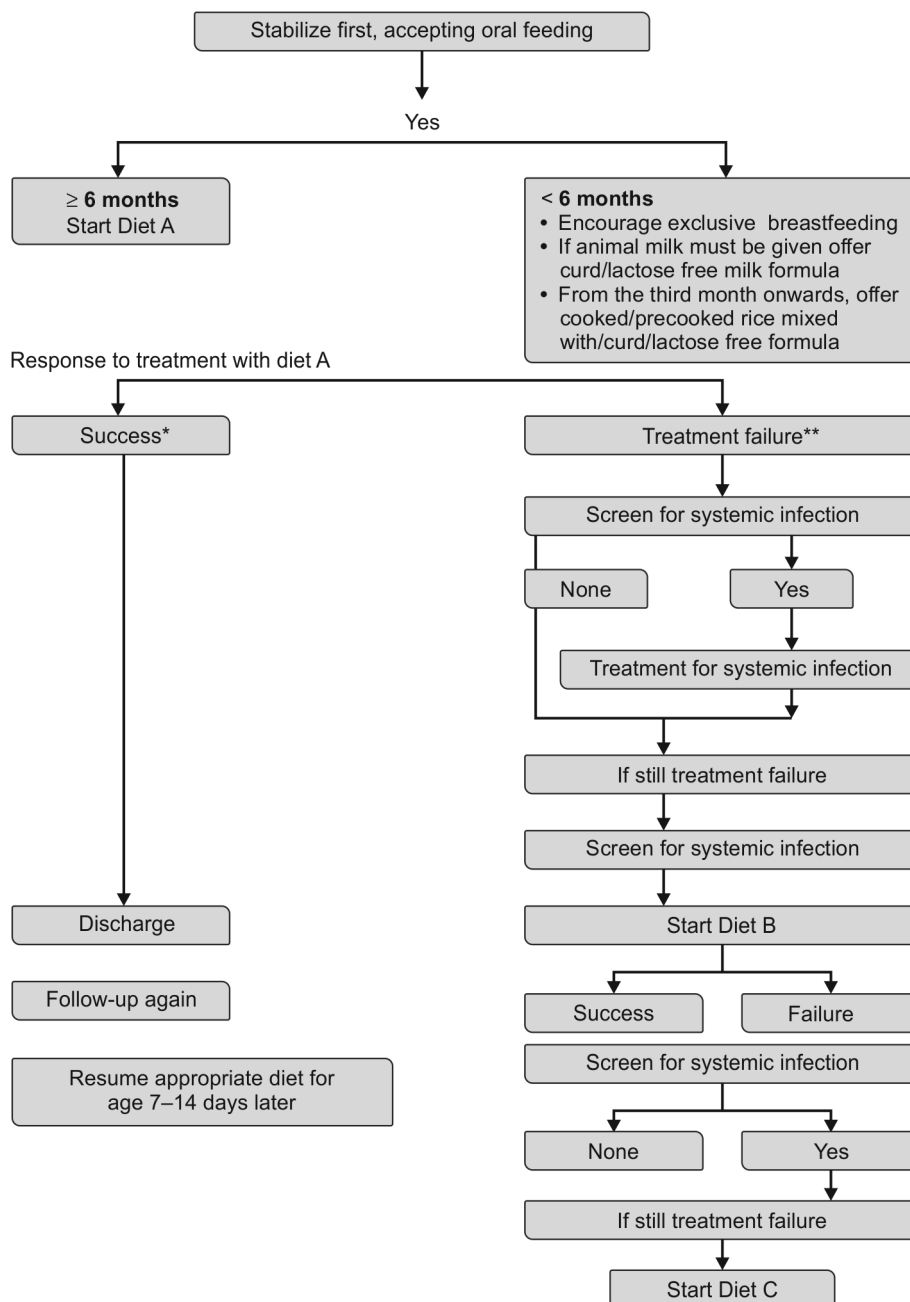
Initial evidence showed therapeutic benefits with locally prepared reduced lactose feeds (modest amounts of milk mixed with cereals or rice lentil yogurt gruels) as compared with complex lactose free diets. Milk or curd cereal mixtures were more efficacious than soy based formulae in clinical trials. These studies clearly showed that total elimination of milk is not required for initial management of PD. The scientific rationale for replacing milk partially with locally available cereals was because it reduces the lactose concentration in the diet without compromising on the protein and the micronutrient content of the diet. Additionally,

Flow chart 1 Algorithm for the treatment of persistent diarrhea in outpatients



*For severely ill children, if referral is impossible, advice to give additional intramuscular gentamicin.

Abbreviations: BF, breastfed; NBF, non-breastfed; FRU, first referral unit; WHO, World Health Organization; ORS, oral rehydration solution; WFH, weight for height

Flow chart 2 Algorithm for dietary treatment of persistent diarrhea in hospital setting

*Successful treatment with either diet is characterized by weight gain, adequate food intake, diminished number of diarrheal stool (≤ 2 liquid stools/day for 2 consecutive days), and disappearance of any fever

**Treatment failure is defined as: in the absence of initial or hospital acquired systemic infection there is:

- A marked increase in stool frequency (usually more than 10 watery stools/day) any time after at least 48 hours on the diet or,
- Return of signs of dehydration any time after initiating treatment or,
- Failure to establish weight gain by 7 days.

Give vitamin A 200,000 IU (>12 months) or 100,000 IU (6–12 months) routinely. For children <8 kg (irrespective of age) administer 100,000 IU. Give mixture of vitamins and minerals providing at least two RDA. If other minerals are difficult to provide, at least give elemental zinc 10 mg daily up to 1 week after recovery. Give antibiotics for bloody diarrhea/systemic infections/severe malnutrition. Diet C is best administered in a hospital with appropriate facilities.

Patients discharged on diet B should be given small quantities of milk as part of a mixed diet after 10 days. If there are no signs of lactose intolerance, increase milk gradually over the next few days.

cereals delay gastric emptying and facilitate better absorption of the lactose in the milk.

Based on this initial evidence WHO tested a two-step dietary algorithm in Asia and Latin America in children with PD. The initial

diet (Diet A) was a reduced lactose milk cereal mix, prepared by replacing milk partially with locally available cereals and legumes. The second level diet consisted of lactose free diet prepared with local staples, where the milk was replaced with an alternative

protein (egg/chicken/legumes—diet B). The recovery rate with diet A was 65% and after diet B was 80%.

The WHO recommended dietary algorithm with clear definitions of treatment failure, that indicated the need for change in diet and a well-defined screening protocol for associated systemic infections, was an important milestone in the management of PD. The recommended diets maintained or increased energy and protein intake, and also improved stool consistency due to higher fiber intake. These diets could be prepared easily at home, and since were highly palatable, were consumed in large amounts, and resulted in faster weight gain. Only a small proportion who did not recover on reduced lactose or lactose free diets required more complex sucrose or even carbohydrate free diets.

The dietary algorithm is currently the accepted standard treatment for PD globally and particularly in the low- and middle-income countries. It has been part of the National Guidelines for the management of persistent diarrhea in India for over two decades. Further, early evidence showed that homemade modular diets (chicken mince with oil and sugar) had significant therapeutic benefits as compared to semielemental formulae making treatment of more complicated PD easier. Use of locally available homemade diets has important public health implications in resource limited settings. The detailed treatment algorithm for the management of PD is provided later.

The initial Diet A (Reduced lactose diet; milk rice gruel, milk rava/sooji gruel, rice with curds, dalia) Total elimination of animal milk is not required routinely. Daily intake of milk should be limited to 50–60 mL/kg providing not more than 2–2.5 g of lactose/kg/day. It is not recommended to reduce the lactose concentration in animal milk by diluting milk with water as it reduces energy density critically. Milk should be mixed with cereals, e.g., some examples are milk or curd rice gruel, milk rava gruel, or dalia (**Table 1**). Feeding should be started as soon as the child can eat. In the beginning 6–7 feeds per day providing a total daily energy intake of 110 kcal/kg/day should be offered. The energy intake should be increased gradually up to 150 kcal/kg/day over the next 2 weeks if required to achieve weight gain. Many children may eat poorly in the initial 24–48 hours because of possible existing serious systemic infection and the appetite will improve as the infection is treated. In situations where there is severe anorexia nasogastric feeding is recommended.

The second Diet B (lactose-free diet with reduced starch) Some children do not respond well to the initial low lactose diet. They may have impaired digestion of starch and disaccharides other

Table 1 Preparation of the initial reduced lactose Diet A

Ingredients	Approximate quantity
Milk	40 mL
Sugar	2 g
Oil	2 g
Puffed rice powder*	12.5 g
Water	To make 100 mL
Calories/100 g	96 kcal
Proteins/100 g	2.4 g

*Can be substituted by cooked rice or rava/sooji (some examples).

Preparation

- Mix milk, sugar, rice together
- Add boiled water and mix well
- Add oil

Table 2 Preparation of the reduced starch Diet B

Ingredients	Approximate quantity
<i>Example of one diet</i>	
Egg white	15 g
Puffed rice powder*	7 g
Glucose	3 g
Oil	4 g
Water	To make 100 mL
Calories/100 g	78 kcal
Proteins/100 g	2.3 g

*Can be substituted with cooked rice.

Preparation

Whip the egg white well. Add puffed rice powder, glucose, oil and mix well. Add boiled water and mix rapidly to avoid clumping.

Example of another Diet B

Ingredients	Approximate quantity
Chicken	7 g
Puffed rice powder*	7 g
Glucose	3 g
Oil	4 g
Water	To make 100 mL
Calories/100 g	78 kcal
Proteins/100 g	2.3 g

*Can be substituted with cooked rice.

Preparation

Boil chicken, remove the bones and make chicken puree. Mix chicken puree with rice, glucose and oil. Add boiled water to make a smooth paste.

than lactose. Children who do not improve on the initial diet A should be given diet B, which should be milk (lactose) free and should provide carbohydrates as a mixture of cereals and glucose (**Table 2**). Milk protein can be replaced by chicken, egg or protein hydrolysate and the starch can be reduced by partially substituting it with glucose. Replacing only part of the cereal with glucose increases the digestibility without resulting in a highly osmolar diet, which would be the case if all the cereals were to be replaced by glucose.

The third Diet C (monosaccharide based diet) Overall 80–85% patients with severe persistent diarrhea will recover with sustained weight gain on the initial diet A or the second diet B. A small percentage may not tolerate a moderate intake of the cereal in diet B. These children should be given the third diet (Diet C), which contains only glucose and a protein source as egg or chicken. Energy density should be increased by adding oil to the diet (**Table 3**).

Monitoring the Response to Treatment

Most children will lose weight in the initial 1–2 days, and then show steady weight gain as associated infections are treated and diarrhea subsides. The weight should increase on at least 3 successive days before one can conclude that weight gain is occurring. Successful treatment is characterized by diminished number of diarrheal stools (less than or equal to two liquid stools day for 2 consecutive days), adequate food intake, and weight gain.

Table 3 Preparation of a monosaccharide based diet (Diet C)

Ingredients	Approximate quantity
Chicken or egg white	12 g
	25 g
Glucose	3 g
Oil	4 g
Water	To make 100 mL
Calories/100 g	60 kcal
Proteins/100 g	3 g

Preparation

Boil chicken, remove the bones and make chicken puree. Mix chicken puree with glucose and oil. Add boiled water to make a smooth paste.

Or

Whip the egg white well. Add glucose, oil and mix well. Add boiled water and mix rapidly to avoid clumping.

Change from the Initial Diet (Diet A) to the Second Diet (Diet B) or Diet B to Diet C

In the absence of initial or hospital acquired systemic infection, the diet should be changed when there is failure on the treatment which is normally defined as a marked increase in stool frequency (usually more than 10 watery stools/day) any time after at least 48 hours of initiating the diet or, return of signs of dehydration any time after initiating treatment or, a failure to establish weight gain by day 7. Unless signs of treatment failure occur earlier, each diet should be given for a minimum period of 7 days.

Patients with Severe Glucose Malabsorption

Poor outcome on diet C may be due to transient glucose malabsorption. This is a rare complication. These patients are identified by presence of reducing substances in stool when glucose is the only carbohydrate in diet, e.g., oral rehydration salts (ORS) solution. The diarrhea ceases promptly on fasting and intravenous (IV) fluids. The practical approach is to administer IV 10% glucose with electrolytes and continue a diet orally which contains only a source of protein (some examples are chicken, egg white) and oil.

Supplemental Vitamins and Minerals

Since most children with PD are malnourished, about twice the Recommended Dietary Allowance (RDA) of supplemental multivitamins and minerals, should be given daily to all children for at least 2–4 weeks. Iron supplements should be introduced only after the diarrhea has ceased. Zinc should be administered as recommended for treatment of acute diarrhea; 10 mg of elemental zinc should be given to infants 2–6 months and 20 mg to children above 6 months for at least 14 days. Studies evaluating the efficacy of zinc in the treatment of persistent diarrhea conducted in Asian countries where there is moderate to high risk of zinc deficiency have shown that zinc supplementation shortens the duration of diarrhea by around 16 hours. Most commercial preparations are available as zinc sulfate, zinc chloride or zinc gluconate. Vitamin A should be administered in standard where doses clinically indicated.

Additional Recommendations for the Severely Malnourished Infants and Children with Persistent Diarrhea

- A single oral dose of 200,000 IU of vitamin A for children more than 12 months or 100,000 IU for children 6–12 months should be given routinely. Children weighing less than

8 kg, irrespective of their age, should be given 100,000 IU of vitamin A.

- On day 1, 50% magnesium sulfate IM once (0.3 mL/kg up to a maximum of 2 mL) should be given. Thereafter, extra magnesium (0.4–0.6 mmol/kg daily) should be given orally for at least 2 weeks. Injection magnesium sulfate (50% which has 2 mmol/mL) can be given orally as a magnesium supplement mixed with feeds.
- 5–6 mEq/Kg/day of potassium should be administered orally or as part of IV infusion during the initial stabilization period. The usual requirement of 3–4 mEq/kg/day, should be continued for at least 2 weeks.
- The other multivitamins and micronutrients should be given as recommended in the treatment of severe malnutrition.

Resumption of Regular Diet

Children on Diet A should gradually resume a diet appropriate for age after 7–14 days. Children on diet B should be given small quantities of milk as part of a mixed diet after 10 days. If they have no signs suggestive of lactose intolerance (diarrhea, vomiting, abdominal pain, abdominal distension, excessive flatulence) milk can be gradually increased over the next few days. A normal diet appropriate for age can be resumed over the next week.

Dietary Management of Persistent Diarrhea in Infants Aged Less than 6 Months

Breastfed infants could normally be passing several soft or mushy stools each day. In such cases, the change in character of stools will be important. Breastfeeding should be encouraged. Mothers who are not breastfeeding should be assisted to re-establish lactation. In cases where only animal milk can be given, curds or a lactose free milk formula should be given with a cup and spoon. From the 6th month onwards cooked/precooked rice can be mixed with milk/curd/lactose free formula.

RECENT ADVANCES

A recent review reported low-to-moderate quality evidence for use of commercially prepared or specialized ingredients compared to home-available ingredients on any outcome in PD. The available evidence does not support the use of proprietary formulas or specialized ingredients over the use of locally produced and readily available foods. This is particularly important in resource constrained settings.

Green plantain or pectin is another intervention evaluated recently in PD. The high content of amylase rich starch (ARS) in the green banana remains undigested in the small intestine of humans, but gets fermented by resident bacteria in the colon into the short-chain fatty acids (SCFA), butyrate, propionate, and acetate. The SCFA stimulate salt and water absorption, and induce a trophic effect on the small bowel and colonic mucosa. It is also postulated to enhance mucosal resistance and promote healing of damaged tissue because of the presence of surface-active phospholipids. Pectin is the amylase-resistant polysaccharides in the cell wall and intracellular substances in green bananas and many other fruits. It contains essentially methoxylated polygalacturonic acids. The pectic substances present in green bananas are mostly α -glucans and dextrin, which hydrolyze into soluble sugars during ripening but are not digested when eaten as unripe fruit. Significant therapeutic benefits on stool output, diarrheal duration and weight gain have been seen with green plantain based diet in studies done in Bangladesh. It was also found to increase the intestinal permeability. Similar results were also reported with pectin. The added advantage of these diets is the low cost and easy local availability.

Potential use of diets made from other locally available ingredients have been explored. Better digestible foods can be

developed by modifying dietary characteristics like the osmolality or the fiber content. One interesting example would be to use amylase-rich flour in decreasing the viscosity and increasing nutrient density of diets. Other such examples need to be explored.

Role of Probiotics

The results of the recent Cochrane systematic review showed insufficient evidence to suggest a beneficial role of probiotics in treating persistent diarrhea in children. Probiotics could have a potential role as a therapeutic agent in the treatment of persistent diarrhea but methodologically well-designed and sufficiently powered trials with different probiotics are required in the future. Effects of one probiotic strain cannot be extrapolated to another one and thus specific probiotic strains and precise dosing of these strains need to be evaluated. Breastfeeding rates, cointerventions and associated comorbidity may influence the therapeutic effects of probiotics making it important to evaluate them in different host and environmental settings.

IN A NUTSHELL

1. Persistent diarrhea (PD) is defined as diarrhea of a presumed infectious etiology that has an acute onset and continues for at least 14 days. It should be differentiated from chronic diarrhea that can last longer and results from congenital, biochemical or metabolic disorders.
2. The risk factors for PD include younger age, malnutrition, irrational antibiotic use in acute diarrhea and lack of breastfeeding.
3. The causative organisms that are isolated from persistent diarrhea stools at higher frequency than in acute diarrhea include Enteraggregative *E. coli*, and *Cryptosporidium spp.*
4. Nutrition is the mainstay of therapy; breastfeeding should be continued; milk should be replaced by reduced lactose preparations such as yoghurt-cereal mix, reduced lactose milk cereal mix prepared by replacing milk partially with locally available cereals and legumes. The second level diet should consist of lactose free diet prepared with local staples, where the milk can be replaced with an alternative protein (egg/chicken/legumes). Supplemental minerals and vitamins should be given to all subjects and rehydration therapy wherever indicated.
5. Antimicrobials are indicated when there is associated dysentery, systemic infection, severe malnutrition or in cases where *Shigella* is isolated from stools.

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Chapter 36.5

Chronic Diarrhea

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Chronic diarrhea, one of the most important cause of failure to thrive (FTT) in infants and children, includes a vast heterogeneous group of gastrointestinal (GI) disorders. The onset may be acute, insidious or intermittent. Elaborate investigations are required to reach to accurate diagnosis. Most of the investigation tools are not available in all the centers in India. The treatment of chronic diarrhea depends upon the underlying cause but at times it is frustrating. This chapter is aimed to elaborate practical approach in the diagnosis and the management of chronic diarrhea.

DEFINITION

Diarrhea is defined as when child passes loose stools more than three times a day. Liquidity of stools is an important component to label as diarrhea. Some authors have stressed upon the weight of the stools; in infants more than 10 g/kg/day, 1–3 years age more than 15 g/kg/day, in older children stool output more than 200 g/day and in adolescents more than 300 g/day as a criteria to define diarrhea. Chronic diarrhea is defined when duration of diarrhea is more than 2 weeks, *irrespective of the etiology*. This is accepted definition in children world over, whereas some authors believe duration of diarrhea for more than 4 weeks in adolescent and adults is appropriate. Infants and children behave differently to diarrheal insults and weight loss occurs very fast hence, growth suffers. At the same time their intake is compromised and adds to the severity of disease. All these factors may not be operating in adults; that is why the duration of 2 weeks is considered appropriate in children. *Persistent diarrhea* also refers to a diarrhea of more than 2 weeks, but it is presumed to be of infectious etiology.

Chronic diarrhea is classified depending upon the age of onset, severity, etiology, organ involved, characteristics of stools and mechanism of diarrhea (**Table 1**).

EPIDEMIOLOGY

The incidence of chronic diarrhea in general population varies from 1% to 5%. The prevalence of chronic diarrhea in young children is unknown in developing countries. According to World Health Organization (WHO) report, every year 2–4 million children die of diarrhea. Diarrhea accounts for 13.2% of all childhood deaths worldwide and 50% are due to chronic diarrhea. Bacterial and parasitic infections are more common in tropical countries whereas inflammatory bowel disease (IBD) occurs more often in western world. Underlying acquired immunodeficiency syndrome (AIDS) has created havoc in both developed and developing countries. Awareness of food allergic disorders is increasing in our country. Cow milk protein allergy (CMPA) is diagnosed in 2–5% of infants with diarrhea whereas celiac disease occurs in 1% population and maximum reported from northwestern states of India.

PHYSIOLOGY OF DIGESTION AND ABSORPTION OF NUTRIENTS

Carbohydrates

Complex starch molecules (amylose and amylopectin) are digested by action of intraluminal salivary and pancreatic amylases. The ingested disaccharides are not absorbed as such. These are broken down by brush border enzymes, e.g., lactase,

Table 1 Classification of chronic diarrhea in infants and children

<ul style="list-style-type: none"> • Age and severity <ul style="list-style-type: none"> – Less than 28 days: Neonatal diarrhea – Age under 1 year <ul style="list-style-type: none"> - Protracted or intractable diarrhea of infancy (PDI/IDI) – Acute infective episodes of diarrhea > 2 weeks <ul style="list-style-type: none"> - Persistent diarrhea – Chronic diarrhea – Well known conditions <ul style="list-style-type: none"> - With or without failure to thrive/malabsorption - With or without villus atrophy
<ul style="list-style-type: none"> • Etiology <ul style="list-style-type: none"> – Organic – Nonorganic (functional)
<ul style="list-style-type: none"> • Organ involved <ul style="list-style-type: none"> – Small bowel – Large bowel – Pancreatic diarrhea – Bile acid disorders
<ul style="list-style-type: none"> • Characteristics of the stools <ul style="list-style-type: none"> – Watery diarrhea – Osmotic – Secretory (nonosmotic diarrhea) – Inflammatory diarrhea – Fatty diarrhea – Toddler diarrhea (chronic nonspecific diarrhea) – Irritable bowel syndrome (diarrhea dominant) – Functional diarrhea – Factitious diarrhea
<ul style="list-style-type: none"> • Mechanisms of diarrhea <ul style="list-style-type: none"> – Secretory diarrhea – Osmotic diarrhea – Deranged motility diarrhea – Exudative/inflammatory/bloody diarrhea

sucrase, maltase, trehalase in proximal small intestine and by glucoamylase in ileum into their monosaccharide molecules, e.g., glucose, galactose and fructose. These molecules enter into the enterocyte through the brush border membrane by carrier molecules. Entry of glucose and galactose, occurs through the carrier protein, sodium glucose linked transporter SGLT1. Entry of sodium occurs along its electrochemical gradient. Sodium blocks glucose exit from the cell and eventually provides the energy necessary for its accumulation in the cell against a concentration gradient. The electrochemical sodium gradient is maintained by Na^+ , K^+ -ATPase located in the basolateral membrane of the enterocyte. Thus glucose and galactose absorption is indirectly active process. Mutations of the gene coding for SGLT-1 are responsible for congenital glucose-galactose malabsorption. The entry of fructose in the enterocytes is through another specific carrier glucose transporter (GLUTs).

Newborns have low amylase activity during the first few weeks of life. Deficiency of various enzymes causes maldigestion of the food. Maldigested carbohydrates are small, osmotically active molecules leading to accumulation of water inside the lumen of the gut. The increased volume of chyme leads to an increased peristaltic activity and a reduced intestinal transit time thereby decreasing the chance of digestion and absorption. In the cecum, the unabsorbed small carbohydrate molecules are readily fermented by colonic bacteria and produce carbon dioxide, hydrogen, methane and lactic, acetic, butyric and propionic acids. Lactic acid, a strong acid, leads to stool pH less than 5.5 and is responsible for perianal excoriation. This low pH disturbs sodium absorption by the colonic mucosa and tends to increase stool volume.

Fats

The digestion of fats starts in the stomach by action of gastric lipase that is active in acidic pH (4.5–5.5). The free fatty acids are released and in the duodenum pancreatic lipase gets adsorbed to lipid droplets resulting in emulsification. In neonate there is low activity of lipase in the pancreatic juice as compared to gastric lipase. The presence of bile salts leads to micelle formation and helps in absorption. During soluble lipid phase, the fat absorption occurs by diffusion through basolateral membrane of enterocytes. Medium chain triglycerides (MCT) do not require micelle formation. MCT gets directly absorbed through apical membrane of enterocytes and reach liver/blood by portal circulation, whereas all other triglycerides, fats and fat soluble vitamins require solubilization and micellization. After absorption in the enterocytes, the chylomicron formation occurs in golgi apparatus. The chylomicrons exocytose from the cell to reach intracellular spaces and are taken up by lymphatics and via thoracic duct to reach circulation.

Fats are hydrophobic so the digestion and absorption of dietary fats are dependent on many other molecules: bile salts, colipase, fatty acid-binding proteins, and apolipoproteins. Fat malabsorption may result from lipase and/or colipase deficiency; abnormal bile salt synthesis, excretion, deconjugation, and reabsorption; impaired triglyceride resynthesis; chylomicron formation and/or excretion; or obstruction of intestinal lymphatics. Isolated fat malabsorption is extremely rare. Bile salts get deconjugated by certain bacterial species in cases of bacterial overgrowth. Unconjugated bile salts are less ionized as compare to conjugated ones at the pH of the gut lumen; thus they have a lower ability to form micelles than the latter. Bacterial overgrowth is associated with other symptoms like: increased degradation of protein and vitamin B₁₂ binding proteins, fermentation of carbohydrates with production of H₂ released in breath and of volatile fatty acids resulting in diarrhea, hypoproteinemia, loss of weight, and megaloblastic anemia.

Proteins

Digestion of proteins starts in the lumen of the stomach, where gastric acid causes denaturation of protein and activates pepsinogens I and II into the pepsins I and II respectively. These are inactive at a pH of less than 5 and have a broad specificity to split the peptide bonds mostly involving phenylalanine, tyrosine and leucine. Food has good buffering capacity so gastric secretion does not play major role in protein digestion. Enterokinase activation leads to conversion of trypsinogen into trypsin, which in turn activates the other zymogens into active proteases. The endopeptidases are serine proteases and have different and strictly defined specific action to release amino acids and peptides. In contrast to carbohydrates, peptides enter enterocytes either after preliminary digestion by brush border peptidases into amino acids or as peptides. In case di- and tripeptides, get entry to the cell these are acted upon by cytoplasmic peptidases inside the cell.

Protein absorption is not affected by gastrectomy. Selective absence of pancreatic protease activities in congenital enterokinase deficiency can lead to protein losses in the stool. The pancreatic exocrine insufficiency leads to loss of nutrients in the stools (fat and starch) resulting in massive steatorrhea. Stool of these patients are often white in color, greasy, soft but not liquid, and extremely foul smelling due to excess of protein content (azotorrhea). In case of mucosal atrophy there is milder form of steatorrhea and protein losses.

The digestion and absorption of various macro and micro-nutrients in GI tract is shown in **Figure 1**.

PATHOPHYSIOLOGY OF CHRONIC DIARRHEA

Four major mechanisms have been proposed:

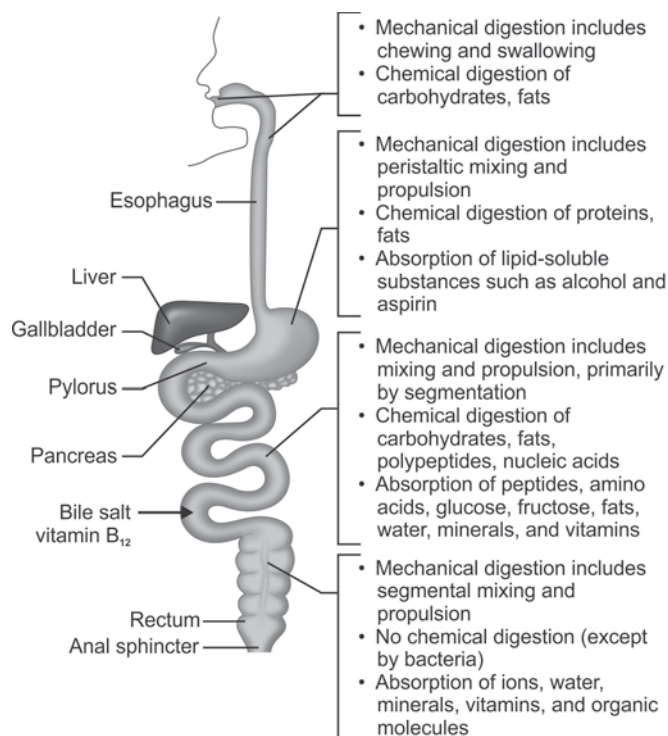


Figure 1 Sites of absorption of various nutrients

Secretion

There is increase in net secretion of electrolyte and fluid from the intestine without compensatory absorption, induced by endogenous secretagogues, even in the absence of an osmotic gradient. Children with a pure secretory type diarrhea will therefore, continue to experience diarrhea even while fasting. Typically, secretagogues affect ion transport in the small and large bowel both by stimulating chloride secretion via cystic fibrosis transmembrane regulator (CFTR) activation. The enterotoxins elaborated by the bacteria, viruses and the parasites interact with the receptors modulating intestinal transport and lead to increased anion secretion. In addition they block specific absorptive pathways.

The intestinal peptides produced by endocrine tumors (e.g., neuroblastoma), e.g., vasoactive intestinal peptide (VIP), calcitonin and the neurotransmitters like acetylcholine, serotonin, histamine and cytokinin produce secretory diarrhea by stimulating epithelial lining. Some drugs and poisons may also affect intracellular transporters and regulators in enterocyte. Two examples of inherited secretory diarrhea are chronic chloride diarrhea (chronic diarrhea) and chronic sodium diarrhea (CSD).

Osmosis

This is caused by the retention of water by the unabsorbed food material in the intestinal lumen. The ingestion of poorly absorbed anions, cations and certain unabsorbed sugars like mannitol, sorbitol, lactulose, lactitol, polyethylene glycol, and fiber diet lead to osmotic diarrhea. Poorly absorbed ions are magnesium sulfate and phosphate. These unabsorbed substances retain water to maintain osmolality equal to body fluids or more. In children secondary lactose intolerance is important cause of chronic diarrhea due to deficiency of lactase enzyme in the brush border of

small bowel. The unabsorbed lactose reaches the colon and leads to osmotic diarrhea. The absorption of electrolytes is not affected so there is not much loss of sodium. The osmotic gap is calculated as $290 - 2 (\text{Stool Na}^+ \text{ Stool K})$. The osmotic gap is more than 100 mOsm/L. The differences between chronic osmotic and secretory diarrhea are given in **Table 2**.

Dysmotility

Chronic diarrhea associated with intestinal dysmotility typically occurs in the setting of intact absorptive abilities. Intestinal transit time is decreased, the time allowed for absorption is minimized, and fluid is retained within the lumen. The high amplitude propagated contractions play a key role in motility disorders of the gut and have been found to be more frequent in patients with diarrhea predominant irritable bowel syndrome (IBS). Although diarrhea predominant IBS may be diagnosed in older children and adolescents, toddlers commonly present with chronic nonspecific diarrhea (CNSD). Changes in small intestinal motility also have been implicated in causation of CNSD. Thyrotoxicosis is also associated with increased motility and decreased transit time.

Inflammation

This may encompass all known pathophysiological mechanisms. Inflammation with resultant injury to the intestine may lead to malabsorption of dietary macronutrients and micronutrients which, in turn creates a luminal osmotic gradient. Additionally, particular infectious agents may induce secretion of fluid into the lumen, and blood in the gut may alter intestinal motility. Diseases such as IBD and celiac disease exemplify this mechanism.

Chronic Diarrhea is a Complex Disorder

The mechanism of diarrhea cannot be explained on the basis of osmotic and secretory pathophysiology alone. There are other factors which are responsible for chronic diarrhea. These are paracrine, immune, neural and endocrine modulators—a regulatory system abbreviated as PINES (**Fig. 2**). They affect the epithelial and smooth muscle functions of intestines and are responsible for diarrhea. The maladaptive responses are responsible for chronic diarrhea. The dysregulation of this system in gut is the main cause for the vicious cycle of chronic diarrhea with or without malabsorption.

ETIOLOGY

Chronic diarrhea is a symptom complex of varied etiologies and caused by heterogeneous group of disorders in children. Various

Table 2 Differences between the chronic osmotic diarrhea and secretory diarrhea

Characteristics	Osmotic	Secretory
Perianal redness	Present	Absent
Volume of stools	< 200 mL/24 hours	> 200 mL/24 hours
Purge	Watery stools, explosive and lots of gas	Watery nonexplosive and no gas
Response to fasting	Diarrhea stops	Diarrhea continues
Stool sodium	< 70 mEq/L	> 70 mEq/L
Reducing substances	Positive	Negative
Stool pH	< 5.5	> 5.5
Osmotic gap	> 100	< 50

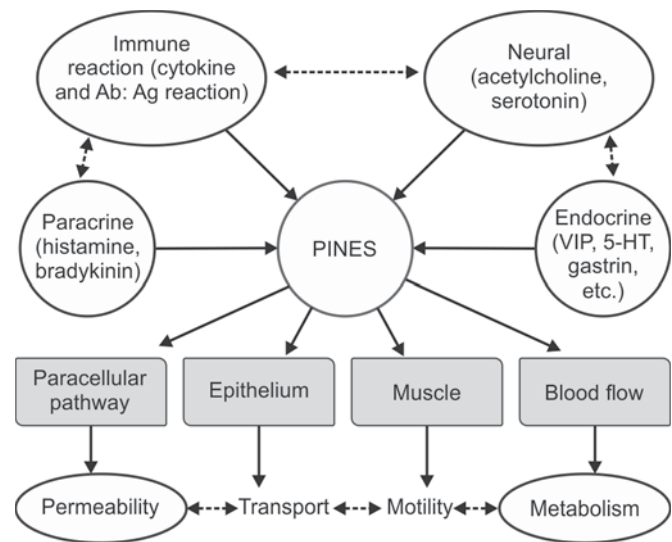


Figure 2 Paracrine-immune-neuroendocrine system (PINES) regulatory system in the gut

causes of chronic diarrhea are given in **Table 3**. The published data from PGI, Chandigarh revealed protracted diarrhea 33%, celiac disease 26%, parasites 9%, CMPA 6%, tuberculosis 5%, cystic fibrosis (CF), short gut and acrodermatitis enteropathica 8%, and unknown 13%. This pattern is similar to report from the west.

Chronic diarrhea needs to be differentiated from fecal soiling, pseudodiarrhea, encopresis, and fecal incontinence where there is uncontrolled passage of the stool in the clothes leading to embarrassing situation for the child and parents. Often parents confuse this with chronic diarrhea but stools are of normal consistency and there is no FTT.

CLINICAL FEATURES

The exact clinical manifestations depend upon the etiological cause of diarrhea and the location of the disease in the GI tract. Broadly they are classified depending upon the involvement of either the small bowel or the large bowel. The differences are shown in the **Table 4**.

APPROACH TO A CHILD WITH CHRONIC DIARRHEA

The approach to evaluate the type of chronic diarrhea is given in **Flow chart 1**. First step is to categorize the type of chronic diarrhea and second step is to investigate for the etiology of chronic diarrhea.

History

It is mandatory to know the characteristics of the stools and duration of diarrhea. The perception of the child and parents about the stools may be different. Confirm whether there is diarrhea or normal stooling pattern or incontinence or encopresis.

Age of Onset

It is important to know the age of onset of diarrhea. There are distinct conditions causing chronic diarrhea and start at different age groups.

Characteristics of Stools

The characteristics of the stools, the frequency, and bulky stools, difficult to flush, with visible oil droplets, undigested food material, with or without blood or mucus are important indicators of underlying disease states.

Table 3 Causes of chronic diarrhea in children

Infections
Bacterial: <i>Shigella</i> , <i>Salmonella</i> , <i>Yersinia enterocolitica</i> , <i>Escherichia coli</i> , <i>Clostridium difficile</i> , <i>Campylobacter jejuni</i> , <i>Vibrio cholerae</i> , <i>Mycobacterium avium complex</i>
Viral: <i>Rotavirus</i> , <i>Adenovirus</i> , <i>Astrovirus</i> , <i>Torovirus</i> , <i>Cytomegalovirus</i> , <i>HIV</i>
Parasitic: <i>Giardiasis</i> , <i>Entamoeba histolytica</i> , <i>Cryptosporidium</i> , <i>Isospora</i> , <i>Strongyloides</i>
Fungal infections
Postenteritis syndrome
Small bowel bacterial overgrowth
Tropical sprue
Diarrhea with excessive intake of: Carbonated fluids, dietetic foods containing, sorbitol, mannitol, xylitol, antacids or laxatives containing lactulose or $Mg(OH)_2$, methylxanthine-containing drinks like cola, tea, coffee, etc., cold beverages like cold drinks including fruit juices, fruits, carbohydrate rich foods, etc.
Carbohydrates malabsorption: Congenital or acquired lactase deficiency, fructose malabsorption congenital or acquired sucrose-isomaltase deficiency, glucose-galactose malabsorption
Abnormal digestion
<i>Pancreatic insufficiency:</i> Chronic pancreatitis, isolated pancreatic enzyme deficiency, hypoplasia of pancreas, cystic fibrosis, Shwachman-Diamond syndrome, Pearson syndrome, trypsin/ chymotrypsin, enterokinase deficiency
<i>Disorders of bile acids:</i> Chronic cholestasis, biliary atresia, neonatal hepatitis, progressive familial intrahepatic cholestasis, use of bile acid sequestrants, primary bile acid malabsorption, terminal ileal resection, etc.
Immune based disorders: Celiac disease, CMPA, food allergy, eosinophilic gastroenteritis, inflammatory bowel disease, autoimmune enteropathy, primary immune deficiency, HIV enteropathy
Structural defects: Lymphangiectasia, microvillus inclusion disease, tufting enteropathy, phenotypic diarrhea, heparan sulfate deficiency, $\alpha_2\beta_1$ and $\alpha_6\beta_4$ integrin deficiency
Defects in electrolyte and micronutrient transport: Acrodermatitis enteropathica, acquired Zinc deficiency, congenital chloride diarrhea, congenital sodium diarrhea, selective folate deficiency, abetalipoproteinemia
Motility disorders: Hirschprung disease, intestinal pseudo obstruction, thyrotoxicosis
Surgical causes: Congenital, acquired short bowel (secondary to stenosis, segmental atresia, malrotation)
Neoplastic diseases: Neuroendocrine hormone-producing tumors: VIPoma, APUDoma, mastocytosis

Abbreviations: HIV, human immunodeficiency virus; CMPA, cow milk protein allergy; VIPoma, tumors secreting VIP (vasoactive intestinal peptide); APUDoma, tumor arising from an APUD (amine precursor uptake of decarboxylation system) cell.

Table 4 Differences between small and large bowel diarrhea

<i>Clinical features</i>	<i>Small bowel</i>	<i>Large bowel</i>
Frequency	Low to moderate	High
Quantity	Large	Small
Consistency	Liquid/semisolid	Liquid/semisolid
Characteristics	Watery, mushy, bulky, undigested	Blood and mucus/ mucus/bloody
Pain abdomen	May or may not present	Associated
Tenesmus	Absent	Present
Etiology	Bacterial/giardiasis Tuberculosis (TB)/Crohn's disease	Bacterial/amebiasis/ ulcerative colitis, Crohn's disease/TB

Nocturnal Diarrhea

Presence of nocturnal diarrhea denotes malabsorptive diarrhea and increased frequency in case of colitis.

Dietary Factors

Relationship with intake of a particular diet like introduction of top feed (animal milk) suggests CMPA. Relationship with wheat intake and improvement of diarrhea after stoppage of wheat

products suggests celiac disease. Excess of intake of fruits, fruit juices and cold beverages indicates osmotic diarrhea. Ingestion of antibiotics and laxatives intake points towards a particular diagnosis. Intake of fat rich diet worsens diarrhea in case of pancreatic insufficiency. Relationship with intake of meals suggests gastrocolic reflux. This may be normal in breastfed infants during first 6 months of life.

Deficiency of Nutrients

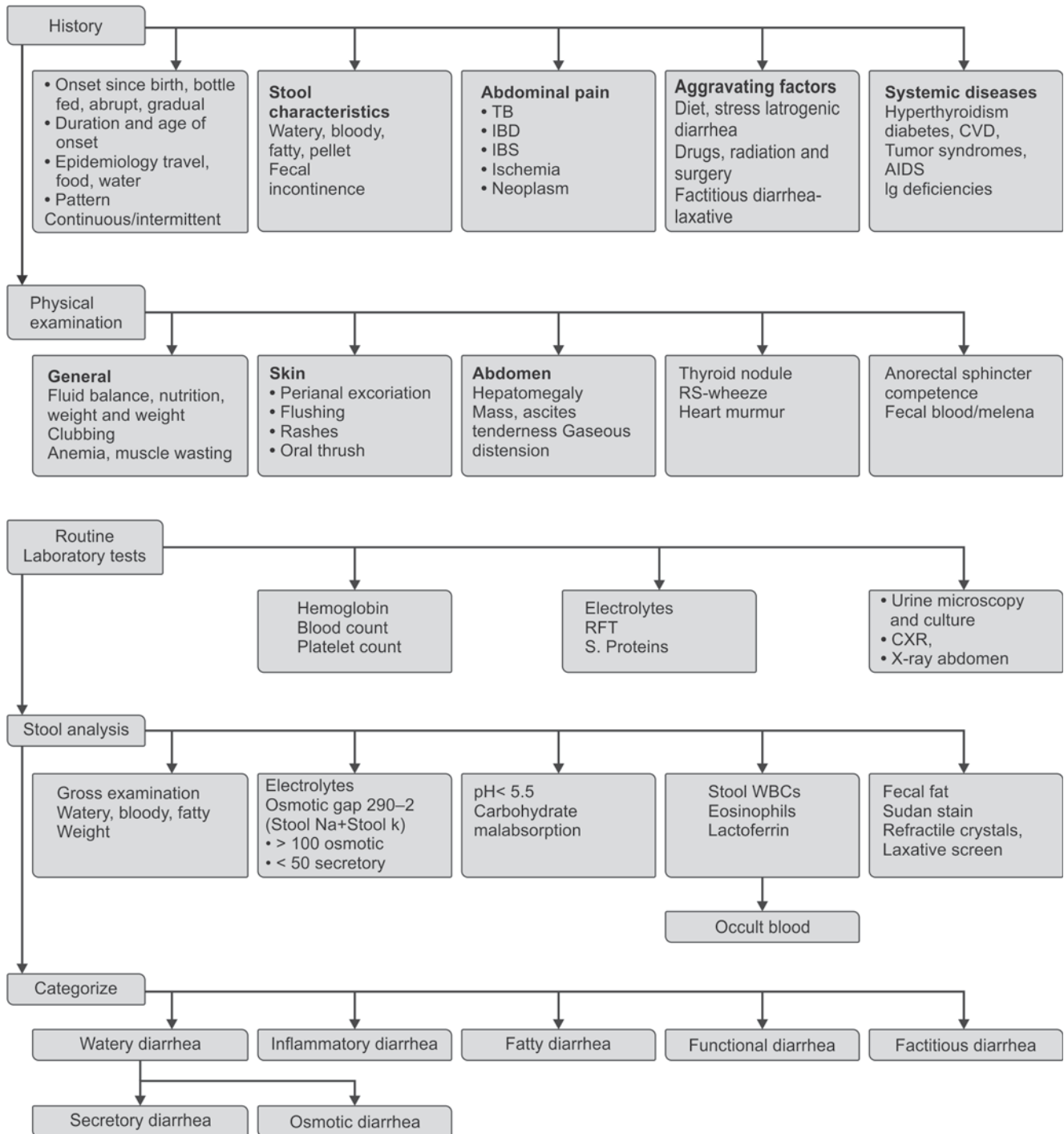
Anemia, rickets, vitamin A deficiency and vitamin B complex deficiency suggests malabsorption and will be associated with FTT. Normal growth with increased frequency of stools suggests diarrhea without FTT.

Pain Abdomen

History of significant pain abdomen is associated with tuberculosis, Crohn's disease, immunoproliferative small intestine disease (IPSID) and chronic pancreatitis. Mild discomfort with bloating can happen with malabsorption and lactose intolerance.

Extraintestinal Manifestations

Multiple systemic symptoms suggest immunodeficiency states, recurrent respiratory infections in cystic fibrosis, asthma and atopic dermatitis in food allergy and joint pains, red eyes, oral ulcers, pyoderma gangrenosum in IBD.

Flow chart 1 Practical approach to chronic diarrhea

Abbreviations: TB, tuberculosis; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; AXR, abdominal X-ray; RFT, renal function test; CXR, chest X-ray; RE, routine examination; WBC, white blood cells.

Surgical Treatment

Surgery done in the past will point towards blind loop syndrome, short gut syndrome, bile salt malabsorption and bacterial overgrowth.

Past History

Past history of immune suppression therapy and repeated exposure to antibiotics and cholestyramine helps to reach to

the cause of diarrhea. Recent history of acute diarrhea will point towards postenteritis syndrome. Any treatment taken in the past should be elaborated.

Family History

Family history is usually positive in autoimmune and allergic disorders. Polyhydramnios is associated with congenital chloride or sodium diarrhea.

Early Life Diarrhea

Intractable diarrhea during first few months of life suggests genetic diseases or transporter defects.

Physical Examination

Obtain a detailed *anthropometry* and plot on the growth charts to see the extent of malnutrition in terms of wasting or stunting with or without edema. See for the signs of *dehydration* if there is acute exacerbation of diarrhea, vomiting and poor intake. Look for *deficiency signs* like pallor, koilonychia, flat or spooning of nails, rickets, cheilitis, glossitis, bitot spots, conjunctiva/corneal xerosis, cutaneous bleed and peripheral neuropathy. Pedal *edema* or anasarca is associated with hypoproteinemia. *Clubbing* is seen in cystic fibrosis, Crohn's disease, celiac disease, and tuberculosis. Look for skin changes like dry, scaly skin, phrynoderma, dermatosis, and recurrent bacterial or fungal skin infections. Oral thrush may suggest human immunodeficiency virus (HIV) infection, exposure to antibiotics and severe malnutrition. Perianal area may show excoriation in lactose intolerance, zinc deficiency and fungal infection. Abdominal examination is done to look for the gaseous distension, ascites, organomegaly, any abdominal masses, previous surgical scars, hernial orifices and genitalia.

Categorize whether chronic diarrhea is small bowel or large bowel in origin. The salient points of differentiation are given in **Table 4**. It is also important to ascertain whether the diarrhea is due to maldigestion or malabsorption. The differentiating points between these two are given in **Table 5**.

Investigations

The tests should be disease specific, easily available and cost-effective.

Hematology

It is very important to define anemia and its types like microcytic hypochromic or macrocytic, megaloblastic or dimorphic. High platelets are seen in iron deficiency anemia like celiac disease and in IBD. Acanthocytes in peripheral smear give clue to abetalipoproteinemia. Erythrocyte sedimentation rate (ESR) and leukocytes are raised in inflammatory conditions whereas lymphopenia suggests intestinal lymphangiectasia. Raised prothrombin time (PT), low prothrombin index (PTI) and high international normalized ratio (INR) indicate vitamin K deficiency in malabsorption syndrome (MAS) and associated liver disease.

Biochemistry

Biochemical tests required are serum proteins, albumin, calcium, phosphorus, electrolytes and renal functions. Liver function tests are done in case of associated liver disease. Anemia due to iron deficiency can be confirmed by measuring serum iron, total iron binding capacity and serum ferritin levels. Vitamin B₁₂ and folic acid deficiency in megaloblastic anemia can be defined by their estimation in the blood.

Table 5 Differentiation between malabsorption and maldigestion

Features	Malabsorption	Maldigestion
Stool fat	++	+++
Fatty acid crystal	+++	-
Flatulence	++	-
Anemia	++	-
Hypoalbuminemia	++	-
Stool volume	++++	++

Stool Examination

Naked eye examination of stool is important whether stools are watery, malabsorptive, bulky, with or without undigested matter, greasy (oil in the stool), blood and mucus. Microscopic examination is done for ova and cyst of parasites, fat globules and fatty acid crystals. For detection of ova and cysts, stool microscopy should be done for 3 consecutive days and this improves the pick rate to 80–90%. *C. difficile* infection is diagnosed by doing *C. difficile* toxin assay and culture sensitivity. Giardia antigen can be detected by ELISA in the stool. Specific polymerase chain reaction (PCR) study can detect various kinds of opportunistic infections especially in immune compromised hosts. Osmotic gap more than 100 mOsm/L indicates osmotic diarrhea and less than 50 mOsm/L in secretory diarrhea. Presence of occult blood in stool is important to define invisible blood loss when anemia cannot be explained, this may be positive in celiac disease. Fecal elastase and chymotrypsin are estimated in stools and their concentration is reduced in pancreatic insufficiency.

Lactose Intolerance Test

Lactose 2 g/kg (maximum of 50 g) is given orally after overnight fasting, glucose sample basal and every 30 minutes or/and breath hydrogen sample (basal and half hourly for 3 hours) are taken. A blood glucose rise of less than 20 mg/dL over basal at 30 minutes or breath H₂ rise more than 20 ppm is taken positive and confirms the diagnosis. However, in an infant and young child these tests are technically difficult and can induce profuse severe diarrhea resulting in dehydration hence, should not be attempted.

Hydrogen Breath Test

The hydrogen is produced by bacteria by fermentation of unabsorbed carbohydrates normally and in case of bacterial overgrowth syndrome. The hydrogen produced by bacteria is absorbed through the wall of small and large intestine or both and reaches the lungs through blood and gets exhaled. The exhaled hydrogen can be measured by gas chromatography. Estimation of fasting breath hydrogen is required before performing breath test. Lactulose/glucose/fructose/lactose is used to perform breath test. All the samples of breath are analyzed for hydrogen and methane every 15 minutes for 2–4 hours. Small intestine bacterial outgrowth (SIBO) is diagnosed on glucose hydrogen breath test (H₂BT) showing a rise in breath hydrogen by 12 ppm above the basal. Early peak denotes small bowel bacterial overgrowth and late peak colonic bacterial overgrowth. However, gold standard test is culture of jejunal aspirate showing bacterial colonic count more than or equal to 10⁵ CFU/mL.

Fecal Fat

Fat malabsorption can be suspected when the fat globules on Sudan III stain are more than 100 per HPF in the stool. It is a crude method to define steatorrhea. The Van De Kamer method is the gold standard to measure 24 hours excretion of fat in grams. The fecal fat excretion is determined by supplementing fat 2 g/kg per day under 2 years of age and 50 g daily in children above the age of 2 years. Fat is given for 3 days and the same time stools are collected and fecal fat is measured. The fat excretion more than 4.5 g/day in children whereas in adolescents and adults more than 6.5 g/day is labeled as steatorrhea, however it is a messy and cumbersome method. Steatocrit is simple and can be easily performed to define steatorrhea. It is done by centrifuging the stool with or without acid and is calculated fat layer (FL)/(FL + solid layer) × 100. Fecal fat is calculated by formula = [0.45 (Acid Steatocrit %)]–0.43 g/24 hours. It is having low sensitivity and specificity as compared to van de Kamer method.

D-Xylose Absorption Test

This test is abnormal in mucosal disease involving the small intestine. The test is done after overnight fasting. 5 g of D-xylose is given orally and patient is encouraged to drink fluids to maintain the adequate urine output. Urine is collected for next 5 hours to detect d-xylose. 1 hour after the ingestion venous sample is taken to detect d-xylose level in the blood. D-xylose more than 1.25 g or more than 20% of the total in the urine collection and a serum d-xylose concentration less than 20 mg/dL are suggestive of mucosal malabsorption. D-xylose absorption test is normal if disease is predominantly involving distal small bowel. This test may be falsely negative in presence of dehydration, renal dysfunction, delayed gastric emptying, ascites and improper collection of urine.

Schilling Test

This test is done to define B₁₂ deficiency, whether gastric or ileal in origin. A small dose of radiolabeled B₁₂ is given orally and at the same time nonradio labeled 1000 µg of B₁₂ is given intramuscular (IM) as the flushing dose, the later saturates the B₁₂ level in the body whereas radiolabeled B₁₂ is absorbed from intestine and is excreted in urine. 24 hours urine is collected, if less than 7% of radiolabeled dose is recovered, it suggests B₁₂ malabsorption. Second phase of schilling test is administration of intrinsic factor and normalizes the schilling test in case of pernicious anemia in which there is intrinsic factor deficiency.

Endoscopy

Upper GI endoscopy is required to define changes in the duodenum and gives clue to cause of malabsorption due to the presence of grooving, scalloping of folds, nodularity, decreased height of the folds and mosaic pattern in celiac disease, white pearl like punctate lesions or vesicles due to dilated lacteals in lymphangiectasia and nodularity, deep linear ulceration in Crohn's disease, nodular duodenal mucosa is seen in giardiasis, celiac disease, Crohn's disease, *H. pylori* infection, CMPA, tuberculosis, eosinophilic gastroenteritis and IPSID. Duodenum may be endoscopically normal. Histology of duodenal biopsy is important to give the diagnosis of underlying disease responsible for chronic diarrhea. Narrow band imaging is important to have direct visualization of villus atrophy with the help of endoscope and this can avoid biopsy. Duodenal fluid can be aspirated and should be examined for giardia, bacterial culture and α heavy chain. Lower GI endoscopy (colonoscopy) is very important to make diagnosis of CMPA, ulcerative colitis, Crohn's disease, tuberculosis, amebiasis, *Strongyloides stercoralis*, cytomegalovirus (CMV) or herpes simplex virus (HSV) infection and microscopic colitis (collagenous colitis and lymphocytic colitis). Terminal ileal intubation can help to pick up ileal disease.

Small Bowel Series

Conventional barium meal follow through (BMFT) has been replaced by enteroclysis which is important to evaluate the stricturous lesions in tuberculosis, Crohn's disease, short gut syndrome, malrotation, diverticulum and internal fistulization.

Ultrasonography, Computed Tomography Scan and Magnetic Resonance Imaging Abdomen

These are used to pick up pancreatic pathology like chronic pancreatitis and hypoplasia of pancreas, thickening of the bowel, lymphadenopathy, masses, loculated ascites, fibrofatty changes, and calcification. The diagnosis of tuberculosis and lymphoma can be made by targeted fine needle aspiration cytology (FNAC) from mass and lymph nodes. The encysted fluid can be aspirated to study adenosine deaminase (ADA) in tuberculosis and abnormal cells.

Special Scan and Endoscopic Ultrasound

Malabsorption suspected due to endoscopic tumors like gastrinoma, somatostatinoma and vasoactive intestinal peptide tumor (VIPoma), Indium-III octreotide scintigraphy scan is performed, whereas endoscopic ultrasonography (US) will be useful in cases of tumor of pancreatitis origin in older children.

Specific Tests

Serological tests like antitissue transglutaminase antibody (tTGA), endomysial antibody (EMA) and deamidated gliadin peptide antibodies (DGP) are required to screen celiac disease with high sensitivity and specificity. These serological tests also have prognostic value. Antienterocyte antibodies are done when autoimmune enteropathy is suspected. Immunoglobulin levels, T-cell function, HIV serology, thyroid function tests (TFT), gastrin and other enteric hormone levels and sweat chloride and plasma zinc levels are required in specific situations.

PRACTICAL APPROACH TO CHRONIC DIARRHEA

Investigations should be directed according to the clinical features of the patient and the probability of underlying etiology of chronic diarrhea (**Flow chart 1**). Gunshot approach should be avoided as far as possible.

Chronic Secretory Diarrhea

The approach to chronic secretory diarrhea is given in **Flow chart 2**. Stools should be sent for culture to find out the any bacterial infection. At the same time microscopic examination of stool should be done for ova of worms or cyst of giardia and trophozoite of *E. histolytica* for 3 consecutive days. *Giardia* antigen can be detected in the stool. Special stains should be done to see for *Microsporidia*, *Coccidia*, *Cryptosporidium* and *Candida albicans* depending upon the high index of suspicion. Small bowel endoscopic biopsy, barium meal studies, colonoscopy, US and computed tomography (CT) scan of abdomen should be done to rule out underlying pathology. Cholestyramine given to the patient improves the bile induced diarrhea.

Chronic Osmotic Diarrhea

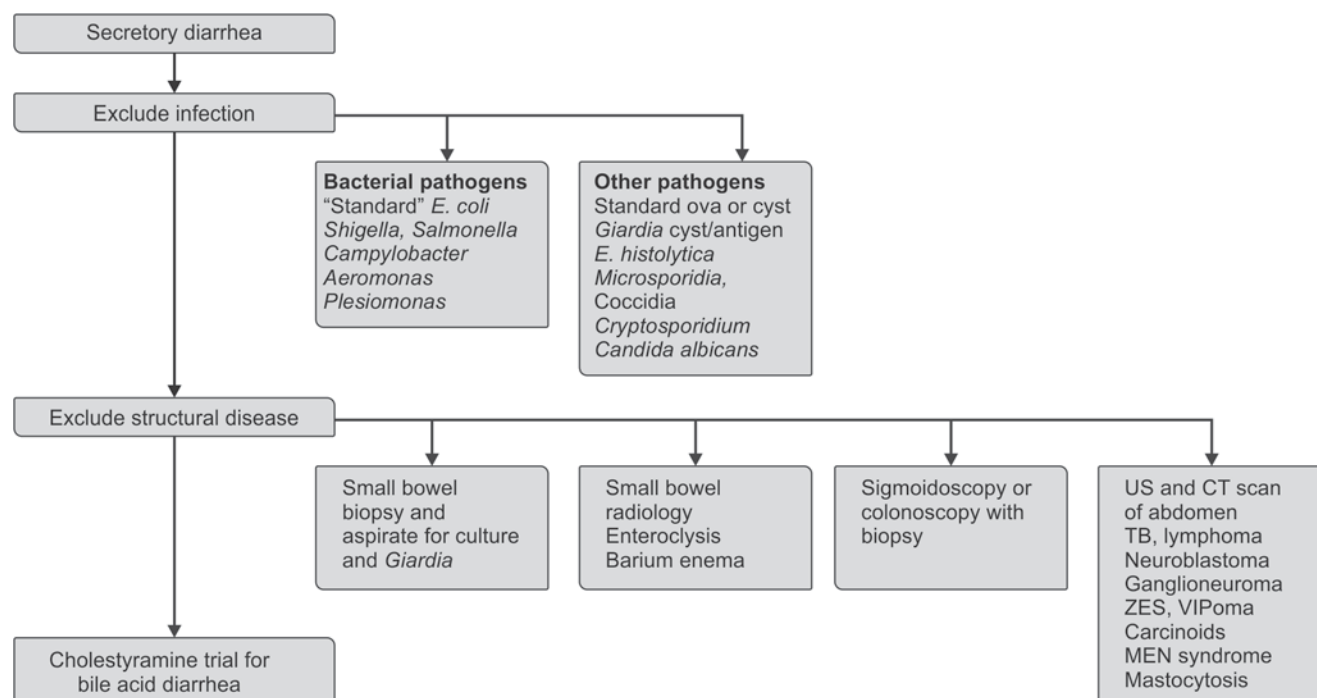
Osmotic diarrhea is characterized by large volume explosive stools and perianal excoriation. Watery stools should be analyzed for reducing substances and pH. Breath hydrogen test with lactose is positive. Lactase enzyme assay can help. Stool can be tested for magnesium and laxative. Reduction in the ingestion of high carbohydrate rich diet improves the diarrhea. Approach is described in **Flow chart 3**.

Fatty Diarrhea

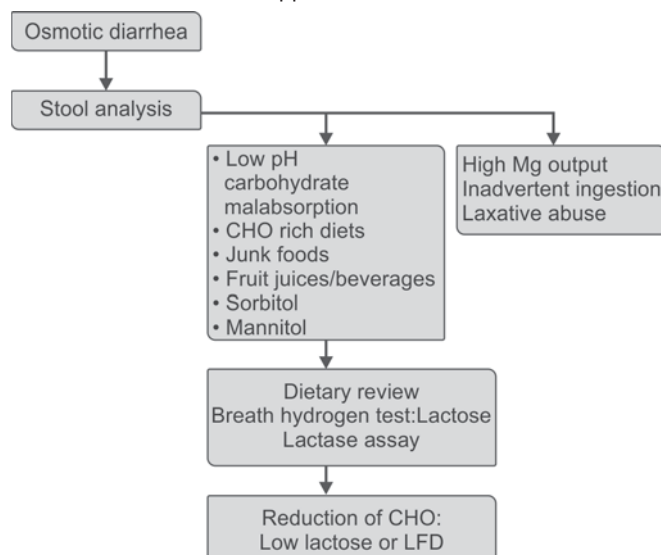
Exclude the mucosal and structural diseases of small intestine. Serological tests for the celiac disease like tTGA, antiendomysial antibodies (EMA), or deamidated gliadin peptide (DGP) antibodies can be performed. If the fecal fat is more than 14 g/24 hours pancreatic causes should be excluded. Different etiologies leading to pancreatic insufficiency may be identified by various tests, e.g., secretin, bentromide tests, stool chymotrypsin and elastase, lipase activity, radio imaging, endoscopic retrograde cholangiopancreatography (ERCP), sweat chloride, bone marrow, etc. Immune profile and HIV serology should be done as and when indicated. Approach is described in **Flow chart 4**.

Chronic Inflammatory Diarrhea

Inflammatory bowel diseases include ulcerative colitis (UC), Crohn's disease and indeterminate colitis. These disorders mainly

Flow chart 2 Approach to secretory diarrhea

Abbreviations: ZES, Zollinger-Ellison syndrome; MEN, multiple endocrine neoplasia.

Flow chart 3 Approach to osmotic diarrhea

Abbreviations: CHO, carbohydrates; LFD, low fat diet

affect the large bowel however Crohn's disease can affect any part of the GIT. Various investigations include small and large bowel biopsy, sigmoidoscopy and colonoscopy, BMFT, barium enema, US and CT scan abdomen. Stool should be cultured, sent for *C. difficile* toxin analysis; larva of *Strongyloidosis*, trophozoite of *E. histolytica*, etc. Exclude viral infections like CMV, herpes and *Candida albicans* in immune suppressed hosts. These infections can exacerbate the UC and Crohn's disease. In our country tubercular colitis should be ruled out. Approach is described in **Flow chart 5**.

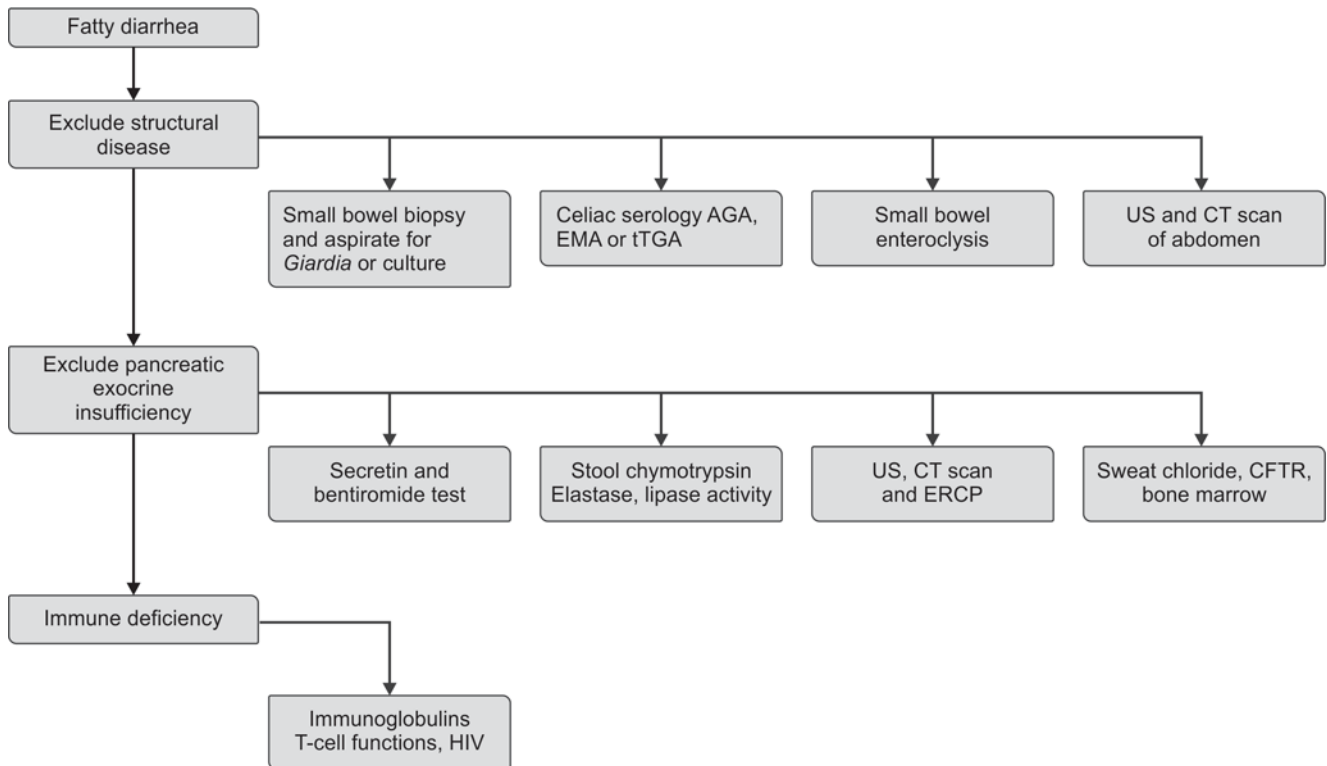
MANAGEMENT

The management of chronic diarrhea is a challenge due to associated multiple nutritional and electrolyte deficiencies, severe malnutrition, associated infections and impact of underlying specific disease state. The treatment of chronic diarrhea is discussed under supportive care and specific treatment of underlying disease leading to chronic diarrhea.

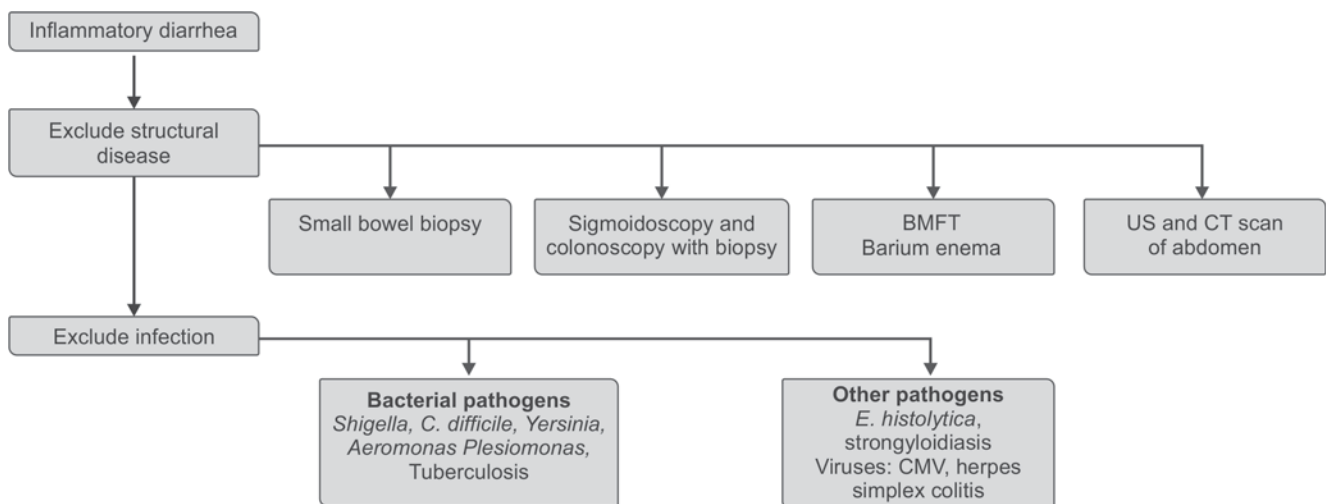
Supportive Care

Supportive care is very important for rebuilding and nutritional recovery. Dehydration is not a problem but acute exacerbation of diarrhea; vomiting and poor intake can lead to dehydration and needs correction with appropriate fluids. Hypokalemia is very common when there is severe malnutrition and need potassium supplementation. Nutrition support plays key role in the outcome. Enteral feeding (per oral or tube feed) should be continued depending upon the acceptability. The introduced diet should be palatable in the form of gruels (mix of cereals, pulses and milk) to begin with. The curd/yoghurt and milk mix diets are tolerated very well. In case of suspicion of celiac crisis patient should be kept on wheat free diet. The diagnosis can be revised later on. In case CMPA is suspected, milk and milk products should be withdrawn. In case of intractable diarrhea during neonatal period or early infancy and short gut syndrome total parenteral nutrition (TPN) is required. Vitamin A deficiency should be treated with three doses of vitamin A given on day 1, day 2 and after 14 days. In case of corneal xerosis, eye care with the help of ophthalmologist is mandatory. Other vitamins deficiency (fat and water soluble) and mineral deficiencies like zinc, iron and calcium should be treated accordingly. Symptomatic hypoalbuminemia should be managed by albumin infusion.

The calories and protein intake should be built slowly to prevent nutrition recovery syndrome also called as refeeding syndrome (RFS). It occurs due to intracellular transfer of

Flow chart 4 Approach to fatty diarrhea

Abbreviations: HIV, human immunodeficiency virus; AGA, antigliadin antibodies; EMA, endomysial antibodies; tTGA, tissue transglutaminase; ERCP, endoscopic retrograde cholangiopancreatography; CFTR, cystic fibrosis transmembrane regulator; US, ultrasonography; CT, computed tomography.

Flow chart 5 Approach to chronic inflammatory diarrhea

Abbreviations: US, ultrasonography; CT, computed tomography; BMFT, barium meal follow through; CMV, cytomegalovirus.

potassium, phosphate and magnesium promoted by increased insulin, cortisol and aldosterone secretion and anabolism induced by high protein and carbohydrate rich diet. The intake of protein tends to stimulate the secretion of hormones and enzymes of the body which are at low ebb. All these are responsible for developing of RFS. The patient develops hypokalemia, hypophosphatemia, hypomagnesemia and the thiamine deficiency. Clinical features of RFS are congestive cardiac failure, arrhythmia, muscle

weakness, hypotonia, altered sensorium, seizure and even death. During dietary management it is important to clinically assess these patients daily including weight for early recognition of this syndrome. Calories and protein should be slowly increased over 1 week. Initially there is weight loss but weight gain is observed after 7–14 days. Early weight gain is an alarming sign of RFS.

The treatment of specific conditions is discussed under description of particular diseases.

SPECIFIC CONDITIONS WITH FAILURE TO THRIVE

Neonatal Onset Intractable Diarrhea

Diarrhea in this age group is severe, intractable accompanied with dehydration, acidosis and malnutrition and associated with significant mortality and morbidity. The causes of neonatal intractable diarrhea are given in **Table 6**. Most often congenital disorders involving the absorption of water, minerals and other nutrients manifest within few hours of birth and the details of each condition are beyond scope of this chapter. The management of the neonate with intractable diarrhea is a challenge. Supportive care and specific antibiotics in case of sepsis are very important. The role of TPN is mandatory especially in transport defects, microvillus inclusion disease, tufting enteropathy or congenital lactase deficiency. Modified enteral feeding is important if gut is healthy and intact. Most of the congenital causes can be salvaged with small bowel transplantation.

Protracted/Intractable Diarrhea of Infancy

This entity requires a special mention among causes of chronic diarrhea in infancy. The criteria of protracted/intractable diarrhea of infancy (PDI/IDI) are (1) diarrhea duration more than 2 weeks, (2) age less than 12 months, (3) no response to conventional therapy and (4) weight loss or no weight gain. The pathophysiology involves the various etiological factors like infection, inflammation, neuroendocrine, diet and their sensitization, medications and toxins, genetic, immunological, vascular, pancreatic, hepatobiliary and other motility disorders. Among all these inciting factors, malnutrition and infection of GI tract play a dominant role leading to PDI. The causes of PDI/IDI in early infancy are elaborated in the **Table 7**. The management consists of supportive care with dietary modification, supplementation of micronutrients, TPN, and small bowel transplantation.

Disaccharidase Deficiency

This is due to deficiency of brush border enzymes like lactase, sucrase, maltase and trehalase present in duodenum and jejunum. Lactase is

Table 6 Causes of neonatal intractable diarrhea

<i>With villus atrophy</i>
Microvillus inclusion disease
Tufting enteropathy
Autoimmune enteropathy
IPEX syndrome: Immune dysfunction, polyendocrinopathy enteropathy and X-linkage
Infections
<i>Without villus atrophy</i>
Congenital villus chloride diarrhea
Congenital sodium diarrhea
Ileal bile acid defect
Galactose glucose malabsorption
Congenital enterokinase deficiency
Intractable due to phenotypic abnormalities
Congenital lactase deficiency
<i>Anatomical defects</i>
Congenital short bowel
Ileal atresia
Microcolon

Table 7 Causes of protracted diarrhea of infancy

<i>Normal villus—crypt architecture</i>
– Transport defects
– Chloride-bicarbonate exchanger (chloride-losing diarrhea)
– Sodium-hydrogen exchanger (congenital sodium diarrhea)
– Ileal bile acid receptor defect
– Sodium-glucose co-transporter (glucose-galactose malabsorption)
– Micronutrient deficiency
– Acrodermatitis enteropathica (zinc deficiency)
– Enzyme deficiency
– Enterokinase deficiency
– Congenital short bowel
<i>Villus atrophy</i>
– Microvillus inclusion disease (MID)
– Tufting enteropathy
– Autoimmune enteropathy
– IPEX syndrome
– Infectious enteropathy
– Postinfectious enteropathy
– Allergic enteropathy
– Cow milk protein allergy
<i>Idiopathic</i>

responsible for digestion of lactose that is the major component of feeding of infants and children. Lactase deficiency is most common as compared to others. The undigested lactose goes down and is acted upon by the colonic bacteria which leads to production of carbon dioxide, hydrogen and methane gases and synthesize short chain fatty acids. These lead to distension of abdomen, flatulence, borborygmi, discomfort and diarrhea. The stools are watery and explosive in nature coming out with a lot of flatus. It is invariably associated with perianal excoriation. There are three types of lactase deficiencies congenital, primary and secondary.

Congenital Lactase Deficiency

This is a very rare and diarrhea starts immediately after intake of milk at birth. There are only case reports in the literature. It is very difficult to manage with lactose free formulae.

Primary Lactase Deficiency

It is also called late onset lactase deficiency or adult type hypolactasia. It is seen in 20–30% older children and adolescents with mild lactose intolerance resulting in chronic diarrhea. Diagnosis is suggested by temporal relationship with intake of milk and typical description of stooling. Stool pH is less than 5.5 and stool reducing substances are positive. Perianal excoriation may or may not be there. Other tests are lactose intolerance and H₂BT. Defining lactase deficiency from duodenal biopsy and genetic studies are not freely available though are gold standard to confirm the diagnosis of adult type hypolactasia. This can be managed by taking milk products in the form of curd or yoghurt and butter milk (*lassi*) and cheese (*paneer*) are well tolerated. Milk alone can cause problems but lactase enzyme (Tablets) can be used before intake of milk. Milk mixed with cereals is well tolerated. Supplementation of vitamin D and calcium is important.

Secondary Lactose Intolerance

Most of the diarrheal episodes are associated with some component of malabsorption of lactose. If acute diarrhea is not treated meticulously, it can get prolonged beyond 7 days. So diarrhea between 7 days and 14 days is a gray zone and leads to maximum damage. The diarrhea is profuse watery with lot of air in the stools. The bottom is sore due to redness caused by acidic nature of the stool leading to perianal excoriation that is very good indicator

of lactose intolerance. Perianal excoriation can be secondary to acquired zinc deficiency and fungal infection. Secondary lactose intolerance is also associated with celiac disease, Crohn's disease, severe malnutrition and giardiasis. The treatment is discussed under persistent diarrhea.

Postinfectious Chronic Diarrhea

Although many infectious causes of diarrhea result in an acute presentation and short course, but some pathogenic bacteria and parasites may cause chronic diarrhea. Viruses rarely cause diarrhea lasting more than 14 days. Rotavirus may cause diarrhea lasting up to 20 days. Acute bacillary dysentery caused by *Shigella* may be resistant to commonly used antimicrobials. This can lead to prolongation of diarrhea due to lingering of underlying infection and lead to chronic colitis. Other bacterial infections like *Yersinia enterocolitica*, Enteroinvasive *E. coli*, Enteropathogenic *E. coli*, *Campylobacter*, *Aeromonas* and *Plesiomonas* can lead to prolongation of diarrhea. *Entamoeba histolytica*, *Giardia lamblia* and *Cryptosporidium* can also cause chronic diarrhea.

Giardiasis

Giardia lamblia causes acute and chronic diarrhea both in healthy and immunocompromised hosts. Infection occurs in duodenum and upper part of jejunum, leading to mechanical effect, disaccharidase deficiency, villus atrophy, bacterial overgrowth and deconjugation of bile salts. All these factors lead to chronic diarrhea and malabsorption. Upper GI endoscopy shows nodularity in the duodenum (Fig. 3). *Giardia* can be detected in duodenal fluid and biopsy. Children can be treated with metronidazole, tinidazole, or nitazoxanide. It is very difficult to eradicate *Giardia* in immune deficient individuals.

Cryptosporidiosis

It can cause infection in immunocompromised and immune competent hosts. In immune incompetent hosts the disease is severe and prolonged. Diagnosis is made by details of oocyst in stools and duodenal fluid. Paramomycin and nitazoxanide are effective to achieve eradication.

Amebiasis

Sigmoidoscopy/colonoscopy shows classical small ulcers with intervening normal mucosa. These small ulcers coalesce to form large deep ulcer and thickness of colon (ameboma). Diagnosis is made by detection of trophozoites engulfing red blood cells (RBCs)

in stools or in the biopsy specimen from colon. Metronidazole is the drug of choice.

Tuberculosis

Tuberculosis is important cause of chronic diarrhea and malabsorption in tropical countries. 15–30% of abdominal tuberculosis may have chronic diarrhea due to tuberculous stricture, ulcerative lesions in bowel, lymphatic obstruction, bacterial overgrowth and malnutrition. Involvement of colon leads to chronic colitis mimicking IBD. The diagnosis is made by Mantoux test, X-ray chest, BMFT (Fig. 4), barium enema (Fig. 5), colonoscopy (Fig. 6) CT (Fig. 7), endoscopic biopsy and FNAC. Antitubercular therapy for 9 months is effective. Sometimes intestinal strictures require stricturoplasty.

Small Intestinal Bacterial Overgrowth

Small intestinal bacterial overgrowth (SIBO) is characterized by malabsorption and overgrowth of bacteria in the small intestine. This is also referred as blind loop syndrome due to recognition of this disorder in patients with predisposing anatomical abnormalities. Classic clinical manifestations are that of malabsorptive state characterized by fatty diarrhea and vitamin B₁₂ deficiency, leading to megaloblastic anemia that is not reversed by intrinsic factor. Gold

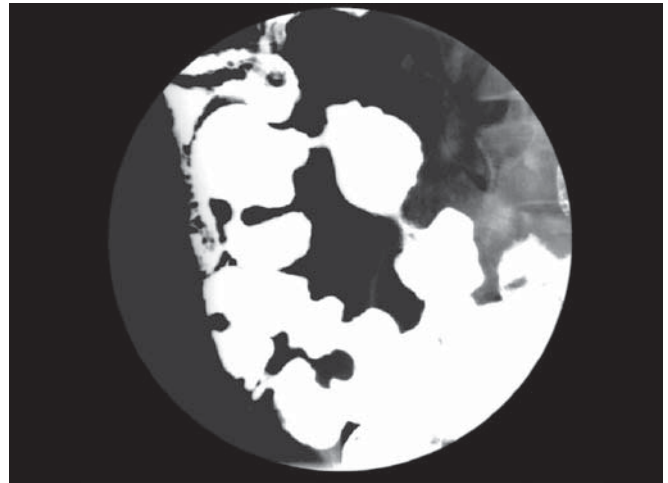


Figure 4 Barium meal follow through (BMFT) showing multiple ileal strictures in tuberculosis

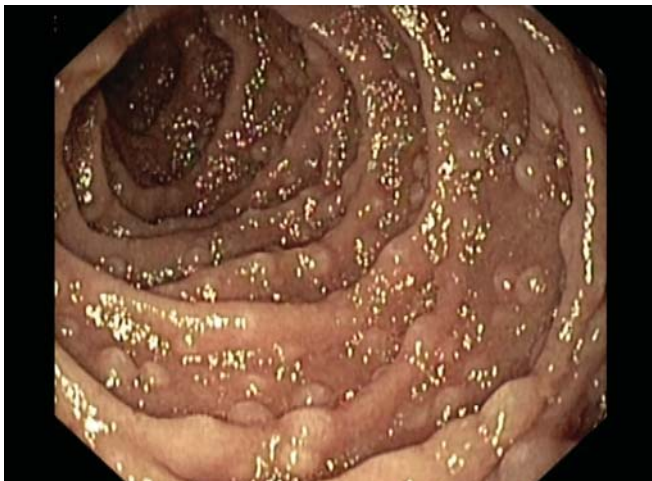


Figure 3 Nodularity in duodenum in a case of giardiasis



Figure 5 Barium enema showing segmental lesions of the colon in a case of tuberculosis

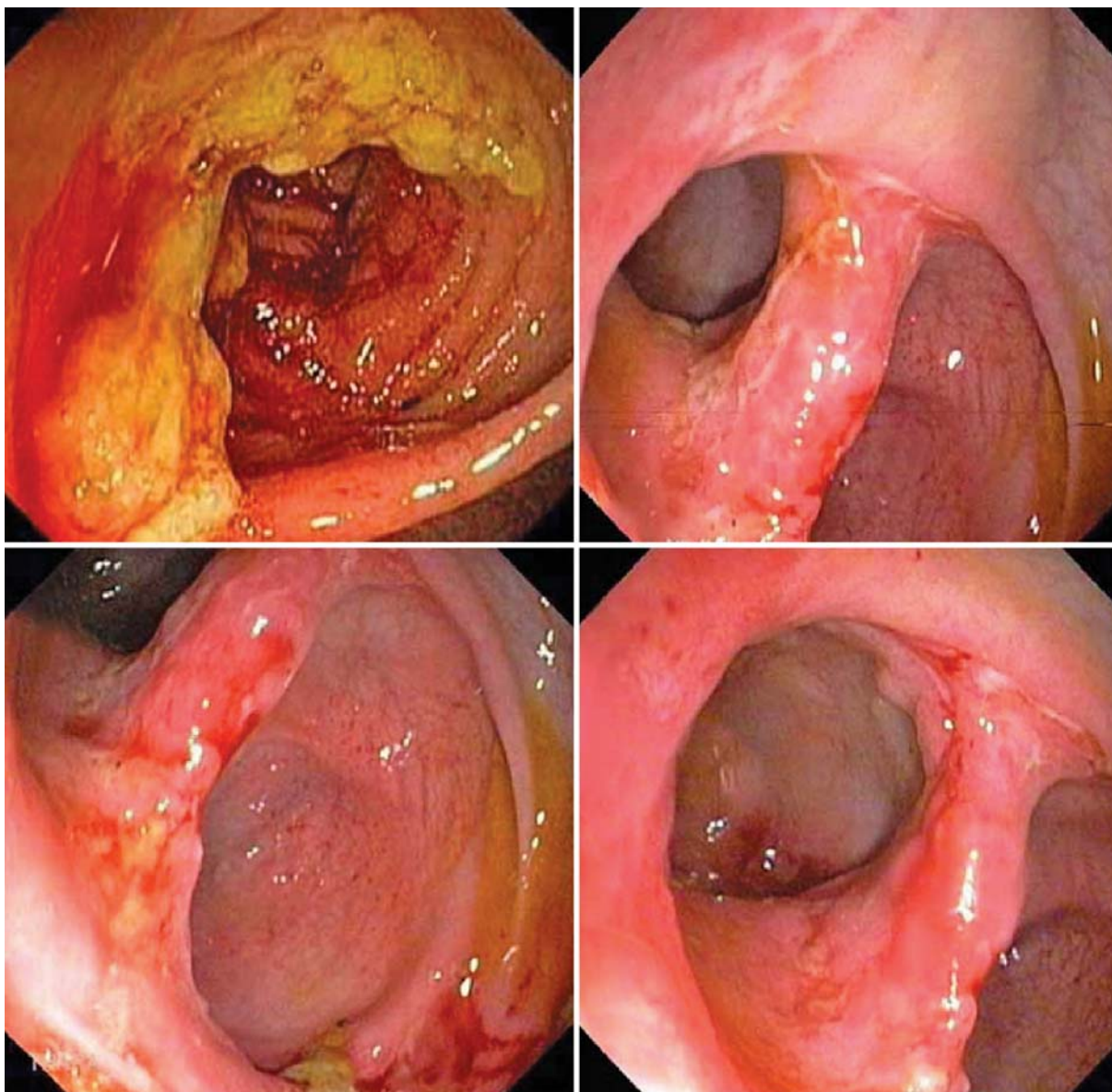


Figure 6 Colonoscopy showing circumferential ulceration of the ascending colon, ileocecal valve gaping with ulceration and thickening and nodularity in a case of tuberculosis

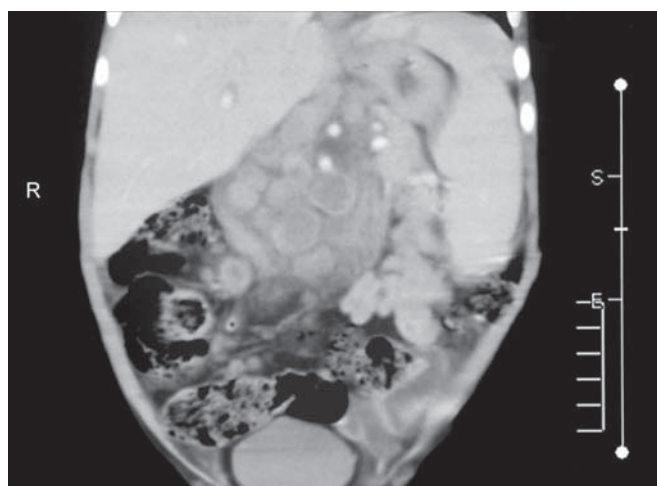


Figure 7 Contrast enhanced computed tomography (CECT) abdomen showing enlarged and necrotic bunch of lymph nodes with hepatosplenomegaly in a case of tuberculosis

standard for the diagnosis is aspirate of small intestinal fluid for culture and bacterial count of more than 10^5 CFU/mL. Treatment includes nutritional supplementation and antibiotic therapy.

Tropical Sprue

Disease of small bowel mucosa due to varied etiology seen mainly in tropical countries including India and Caribbean and this is one of the close differential diagnoses of celiac disease. The disease manifests as chronic diarrhea, malaise, weight loss and malabsorption of various nutrients including vitamin B₁₂ and folate. Onset is typically after an episode of gastroenteritis and there is significant alteration in gut microflora with increase in enterobacteriaceae leading to damage to absorptive surface area culminating in malabsorption. Symptoms usually resolve with supportive care and antibiotics. These days this is less often encountered. Tropical enteropathy results from repeated bacterial infection in tropics responsible for blunting of villi.

Immunoproliferative Small Intestinal Disease

It is a variant of the B-cell lymphoma of mucosa-associated lymphoid tissue (MALT), which involves mainly the proximal

small intestine resulting in malabsorption, diarrhea, clubbing and abdominal pain. Immunologically, IPSID lymphomas reveal excessive plasma cell differentiation and produce truncated alpha heavy chain proteins lacking the light chains as well as the first constant domain. Treatment includes antibiotics and anti-neoplastic agents depending upon the stage and severity of the disease.

Immunodeficiency States

Both congenital and acquired immunodeficiency disorders can cause severe chronic diarrhea in infants and children.

Congenital Immunodeficiency

The most common congenital immunodeficiency disorders leading to chronic diarrhea are X-linked agammaglobulinemia or hypogammaglobulinemia, selective IgA deficiency, common variable immunodeficiency (CVID), severe combined immunodeficiency (SCID) and chronic granulomatous disease (CGD). All these conditions can manifest with intractable diarrhea due to infection by unusual microorganisms. FTT and systemic infections in agammaglobulinemia and hypogammaglobulinemia require supportive care, intravenous (IV) gammaglobulins and antimicrobial therapy. CVID can manifest during infancy and childhood with chronic diarrhea and FTT and treatment is same as in case of agammaglobulinemia. Selective IgA deficiency can manifest with giardiasis, bacterial overgrowth and enteropathy and is prone to celiac disease and Crohn's disease. There is need of treatment of underlying infections. SCID is severe form of disease manifests in the early life and untreated children dies by 1–2 years of age. Bone marrow transplantation can cure the disease. CGD can manifest with chronic diarrhea and multiple abscesses. The treatment is γ -interferon and antimicrobial therapy.

Acquired Immunodeficiency Syndrome

AIDS can manifest with acute and chronic diarrhea with lymphadenopathy and hepatosplenomegaly and patients are prone to multiple bacterial, viral, protozoal and fungal infections. Diagnosis is made by HIV positive and chronic diarrhea count less than 200 cells/mL. Attempt should be made to define microorganism from stool by microscopy, culture, antigen detection and PCR. At times if the infection is not there, chronic diarrhea could be due to AIDS enteropathy. Treatment involves supportive care, specific antimicrobials and HAART. Protease inhibitors can induce diarrhea and should be kept in mind.

Immune Suppressed States

Treatment of leukemia, lymphoma and malignant tumors require specific chemotherapy and radiation. Autoimmune diseases [autoimmune hepatitis (AIH), systemic lupus erythematosus (SLE), AI hemolytic anemia] and liver and kidney transplanted patients are treated with steroids and other immune suppressive drugs. Some of the drugs can induce diarrhea, e.g., mycophenolate mofetil. These drugs lead to immune suppression and make the individual prone to usual and opportunistic infections of gut leading to chronic diarrhea. Attempt should be made to define the microorganism responsible for diarrhea and treat accordingly with antimicrobials and supportive care. Radiation induced enteritis can lead to chronic diarrhea.

Food Allergy

Allergic enteropathy (eosinophilic enteropathy) presents with FTT, vomiting and diarrhea whereas allergic colitis occurs in relatively healthy and well thriving infants. Often allergic colitis is reported with ingestion of cow milk and soybean.

Cow Milk Protein Allergy

Cow milk protein allergy is an immune mediated reaction to milk proteins and occurs after ingestion of cow milk. It has been reported in 2–5% of infants and young children suffering from chronic diarrhea. There are two types of reactions, the immediate and late onset. Immediate reaction is IgE mediated and occurs within minutes of milk ingestion or contact. It is characterized by immediate urticaria, swelling of lips, vomiting, pallor or shock like state. The late onset reaction is a T-cell mediated reaction, occurs after 6–8 weeks of milk ingestion and has indolent course.

The presentation of late onset CMPA can be with GI and non-GI related symptoms. The GI related symptoms occur in 50–60% of cases. These occur in form of proctocolitis in young healthy infants in 2–4 months of age and are characterized by passage of blood and mucus in the stool mimicking late hemorrhagic disease, acute infective colitis or UC. Whereas in older infants and young children present with intractable diarrhea with FTT due to malabsorption. Other manifestations are vomiting mimicking gastroesophageal reflux disease (GERD), chronic constipation, anemia and hematemesis secondary to hemorrhagic gastritis.

The non-GI presentations of CMPA are related to skin and respiratory system. The skin manifestations are atopic eczema, urticaria and angioedema whereas respiratory symptoms are nasal stuffiness, sneezing and chronic cough with wheeze mimicking asthma.

Diagnosis is based on high index of suspicion with temporal relationship of intake of cow milk or top feeding in infants. IgE mediated CMPA can be diagnosed by immediate reactions, positive skin prick test to cow milk protein, a reaction of more than 3 mm and raised specific IgE immunoglobulin. Stool examination shows eosinophils, leukocytes and RBCs whereas culture will be negative to distinguish from infective colitis. The diagnosis of T-cell mediated disease can be made by endoscopy and histology of the biopsy sample. Upper GI endoscopy reveals erosive gastritis (rare) and nodularity in the duodenum and histology of biopsy shows lymphoid hyperplasia, eosinophilic infiltrate and villus atrophy. Sigmoidoscopy will show small superficial ulceration, hyperemia, edema, nodularity, and aphthous ulcers (**Fig. 8**). Histology of biopsy shows lymphoid hyperplasia and eosinophilic (>6/HPF) infiltrate.

The gold standard for diagnosis of food allergy is elimination and challenge test. The symptoms stop after withdrawal of milk and recur within 48 hours of milk intake. Goldman suggested



Figure 8 Sigmoidoscopic picture showing loss of vascular pattern, edema and multiple aphthae in a case of cow milk protein allergy (CMPA)

three such positive challenges for making the definite diagnosis but it is too cumbersome and very difficult to fulfill the criteria. Relationship of clinical symptoms with milk intake, endoscopic findings, and biopsy characteristics, disappearance of symptoms after milk withdrawal and demonstration of normal histology are good enough to make the diagnosis.

Introduction of milk should be done at least after 1 year of withdrawal. In case symptoms reoccur, milk should be stopped and rechallenge after 1 year. If challenge is negative continue with milk and milk products. The management of food allergy is simple, to stop the inciting food. Milk and milk products should be withdrawn from the diet. Soya milk is a very good substitute in India though extensively hydrolyzed formula (EHF) is recommended. Some issues with soya have been raised in the literature but are minor. In case of allergy to soy protein, it should be stopped. Special formulae like EHF are not available in India. In this situation rice gruel is preferred for infants with adequate protein and calories to maintain the health. Supplementation of adequate minerals and vitamins is mandatory. IgE mediated CMPA infants can have problems with EHF and need elemental amino acid formula (AAF). Mother milk should be encouraged. Very rarely cow milk protein through breastmilk may cause problem in the infant, this requires stoppage of intake of cow milk and milk product by the mother while breastfeeding. Infants with late onset reactions outgrow earlier as compared to IgE mediated reactors. More than 90% outgrow from this problem by 2–4 years of age.

Food Protein Induced Enterocolitis Syndrome

It is a rare and T-cell mediated GI food hypersensitivity characterized by intractable diarrhea with blood in the stool, vomiting, anemia, hypotonia, dehydration and hypovolemic shock. In absence of fever presence of eosinophils cells in the stool and negative stool culture help to differentiate from infective colitis. Severe UC should be excluded.

Soya Protein Allergy

Soya protein allergy is uncommon in our country. Isolated allergy is very rare. It has been reported in 10% of cases along with CMPA. The clinical manifestations are similar to CMPA. Diagnosis is by temporal relationship and diagnostic approach is same as in CMPA. Treatment is stoppage of soya based products. Usually infants outgrow and start tolerating after 1 year.

Celiac Disease

This is now defined as an autoimmune disorder that occurs in a genetically predisposed individual who gets sensitized to gliadin a protein moiety of wheat and on withdrawal of wheat there is clinical improvement. The other cereals like barley and rye, cross react to gliadin and produce symptoms of celiac disease. This is the most common cause of chronic malabsorptive diarrhea in children. The classical manifestations are diarrhea, FTT and anemia (**Fig. 9**). The atypical presentations are short stature, constipation, pain abdomen, iron deficiency anemia, diabetes, and dermatitis herpetiformis. Diagnosis is based on the high index of suspicion. The investigations include complete hemogram, type of anemia, D-xylose test, endoscopic duodenal biopsy and serological tests like, anti tissue transglutaminase, endomysial antibodies and deamidated gliadin peptide (DGP) antibodies. On endoscopy there are classical well defined endoscopic markers of celiac disease like grooving, scalloping, nodularity, loss of folds and mosaic pattern (**Fig. 10**). Duodenal biopsy shows varying degree of villus atrophy (Marsh classification). Narrow band imaging shows loss of villi. HLA DQ2 and DQ8 are positive in 98% of celiac patients. Diagnosis and treatment have been detailed in the chapter on celiac disease in the previous Section on gastrointestinal disorders.



Figure 9 Case of celiac disease showing multiple micronutrient deficiencies, stunted growth and pedal edema



Figure 10 Endoscopic view of duodenum showing atrophic folds with grooving, scalloping and mosaic pattern in celiac disease

Intestinal Lymphangiectasia

There is a defect in the lymphatic drainage of small bowel and may be associated with lymphedema of upper or lower limbs. Patients presents with diarrhea, generalized edema, tetany but no anemia. The hypoproteinemia is responsible for edema and occurs due to loss of protein by the rupture of dilated lacteals in the small intestine. The diagnosis is made by upper gastrointestinal (UGI) endoscopy showing pearl like lesions/vesicles in the mucosa and the endoscopic biopsy of the small intestine. This requires withdrawal of triglycerides other than medium chain triglycerides (MCT), hence MCT rich diet is recommended. MCT gets absorbed directly by the enterocytes and go into portal circulation rather than going into lymphatic. The edema and diarrhea disappear, but compliance is a problem.

Abetalipoproteinemia

This is an autosomal recessive disorder due to defective synthesis of apolipoprotein B, making the intestinal enterocyte unable to

couple triglycerides into chylomicrons for systemic transport, leading varied manifestations. Acanthocytes in blood smear is a great clue. Fatty diarrhea is one of the major manifestations apart from deficiencies of other fat soluble vitamins. Treatment includes replacement of triglycerides containing long chain fatty acids with MCT and dietary supplements with tocopherol. In the same group the other disorders which present with fat malabsorption are familial hypobetalipoproteinemia, Anderson's disease, chylomicron retention disease and Wolman disease.

Pancreatic Disorders

Most important pancreatic disorders like chronic pancreatitis, cystic fibrosis and hypoplasia of pancreas are responsible for fatty diarrhea. There are syndromes like Shwachman-Diamond syndrome, Johanson-Blizzard syndrome, isolated pancreatic enzyme deficiency, Pearson syndrome, etc. which are also associated with fat malabsorption. Chronic pancreatitis is characterized by pain abdomen and usually long history and fatty diarrhea develops, when more than 90% of pancreatic tissue is destroyed. Various pancreatic tests described earlier including imaging studies and ERCP confirm the diagnosis. The description of the stools is greasy/oily stools difficult to clean and fat droplets may be noted per-rectum or fat may get separated when stool is kept for some time. In cystic fibrosis, respiratory symptoms dominate; pancreatic insufficiency develops during second decade of life. Pancreatic hypoplasia manifests in early infancy and FTT along with steatorrhea are the main manifestations. Various syndromes manifest with other associated clinical picture. Careful enzyme replacement therapy is helpful to ameliorate the symptoms.

Bile Salt Diarrhea

Conjugated bile salts reach to duodenum for solubilization and micellization. The congenital absorption defect and resection of terminal ileum allow the excess of the bile salts in the colon and cause excess of secretion and watery diarrhea. At the same time lead to fat malabsorption due to decreased bile salt pool in the body. In case of SIBO the bacteria deconjugate the bile salts and these deconjugated bile salts are responsible for cathartic effect and diarrhea. Cholestyramine is effective to bind the bile salts and reduces watery diarrhea symptoms.

Short Gut (Bowel) Syndrome

It occurs when there is a significant decrease in the absorptive surface due to congenital and acquired causes. In children the length of the small and large intestine is 600 cm and 150 cm respectively. Children are mostly afflicted by various congenital malformations, e.g., malrotation leading to volvulus, gastroschisis and due to extensive gut resection in necrotizing enterocolitis and ischemic bowel injury. The exact clinical manifestations depend

upon the extent, site of resection and left over length of gut with or without ileocecal valve. The symptoms occur when small bowel length is less than 170 cm and no colon or small intestine less than 70 cm with intact colon. Limited ileal resection has better clinical outcome. However, the loss of ileocecal valve predisposes to SIBO and its complications. Short gut syndrome can lead to liver disease, renal stones, d-lactate acidosis and gallstones due to prolonged requirement of TPN. Treatment of this condition is supportive care, maintenance of nutrition by enteral or parenteral route. Small bowel transplantation is required when there is extensive resection of the small bowel and nutritional support is inadequate.

Endocrinopathies

Diabetes mellitus (DM), congenital hypoparathyroidism, Di-George syndrome; multiple endocrine neoplasia, Addison disease, mucocutaneous candidiasis, hyperthyroidism, secretory tumors: gastrinoma (Zollinger-Ellison syndrome), somatostatinoma (somatostatin), VIPoma (ganglioneuroma and ganglioblastoma: VIP) and carcinoid: 5-hydroxytryptamine can cause chronic diarrhea. Diarrhea in DM is due to altered bowel motility, SIBO and bile salt malabsorption and celiac disease (10%). It is worth mentioning that all above-mentioned conditions are associated with chronic diarrhea. The diagnosis of underlying conditions depends on diligent search and treatment is disease specific. The tumors need surgical resection.

Cystic Fibrosis

Around 90% of children suffering from CF develop exocrine pancreatic insufficiency and results in malabsorption of nutrients. The condition is discussed in detail in the Section on respiratory disorders. Malabsorption of fat, carbohydrate and proteins is due to loss of exocrine function and involvement of biliary tract. There is deficiency of lipases, amylases and proteases. Maldigestion results in steatorrhea and fecal fat excretion is usually more than 14 g per day. Thick secretions and SIBO also contribute to malabsorption. This is responsible for oily/greasy stools. Oil droplets or separate oil can be seen in stools. Fecal elastase and chymotrypsin levels are very low. Neonate may be born with microcolon or thick secretion/pellets in small and large bowel. Sweat chloride and cystic fibrosis transmembrane regulator (CFTR) gene studies confirm the diagnosis. Treatment is replacement of pancreatic enzymes.

Inflammatory Bowel Diseases

This covers ulcerative colitis, Crohn's disease, and indeterminate colitis and has been discussed in the previous Section on gastrointestinal disorders. Ulcerative colitis involves only the colon. Endoscopic picture is classical and biopsy shows involvement of colonic mucosa (**Fig. 11**). Crohn's disease is more severe, involves whole of the GI tract from oral cavity to rectum. This is a transmural

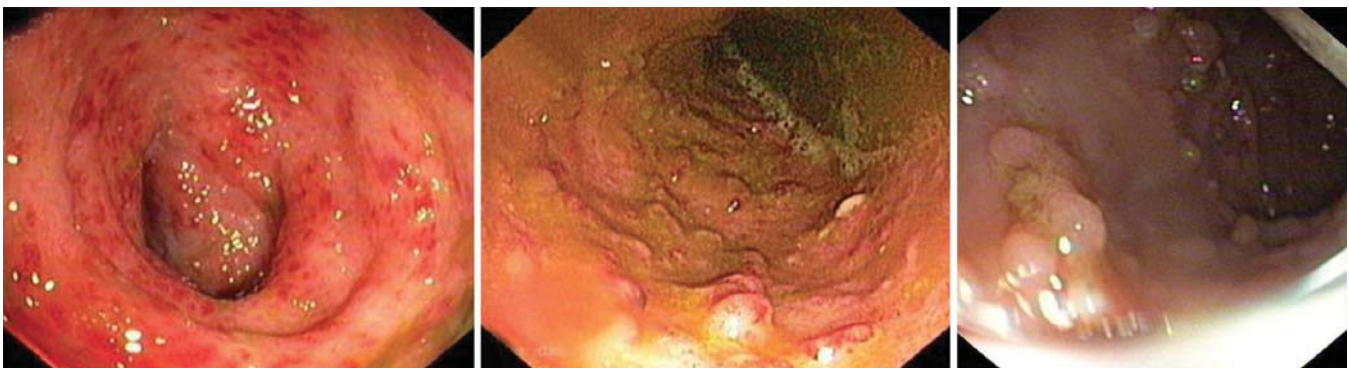


Figure 11 Colonoscopic picture showing acute (ulceration, bleeding, edema, loss of vascular pattern) and chronic (pseudopolyps) lesions in ulcerative colitis

disease involving all layers of gut gives rise to deep linear ulcers and punched ulcer and cobblestone appearance of mucosa and hence leads to perforation and fistula formation (**Fig. 12**). Indeterminate colitis is defined when the condition neither fits with UC nor with Crohn's disease.

Microscopic Colitis

This is an unusual entity recently described as cause of chronic diarrhea in children. Exact etiology is unknown, even though various pathophysiological mechanisms have been postulated. It presents as chronic profuse watery diarrhea with cramping abdominal pain. On colonoscopy the mucosa is absolutely normal; however the histology of biopsy reveals the changes in the form of subepithelial collagenous band in case of collagenous colitis (CC) (**Fig. 13A**) and increased in number of intraepithelial lymphocytes in lymphocytic colitis (LC) (**Fig. 13B**). Biopsy shows inflammatory infiltrates in the mucosa and submucosa. Lymphocytes outnumber the plasma cells in lamina propria. Lymphocytes infiltrate the mucosa and account for 10–25% of all mucosal cells. Treatment includes budesonide, mesalamine and probiotics.

Hirschprung Disease

Chronic diarrhea in Hirschprung disease (HD) during neonatal period and early infancy is a result of enterocolitis due to bacterial stasis in the lumen. Thirty percent of HD during early

infancy develop diarrhea. Infants present with fever, explosive diarrhea, abdominal distension, bleeding per-rectum and perianal excoriation. Diagnosis is suspected by delayed passage of meconium (> 24 hours) after birth that is present in 94% of HD infants. Per-rectal examination is very classical: rectum is empty and on withdrawal of finger there is gush of stool. In older children there is no fecal soiling and withholding maneuver as seen in functional constipation. Barium enema, manometry and rectal biopsy have classical features of HD seen in older children. The treatment of enterocolitis is supportive care and antibiotics. Later on surgical treatment is required.

CHRONIC DIARRHEA WITHOUT FAILURE TO THRIVE

Chronic Nonspecific Diarrhea of Childhood

Chronic nonspecific diarrhea of childhood (CNSD) is the very common form of chronic diarrhea in the preschool years without failure to thrive. This is also called toddler's diarrhea. The typical time of onset may range from 1 year to 3 years of age and can start from infancy until age 5 years. The consistency and the frequency of the stools are different from that of other children. Affected children may pass multiple bowel movements usually 4–10 times per day. Specific to CNSD is the pattern that these patients pass stools only during waking hours, typically beginning with a large formed or

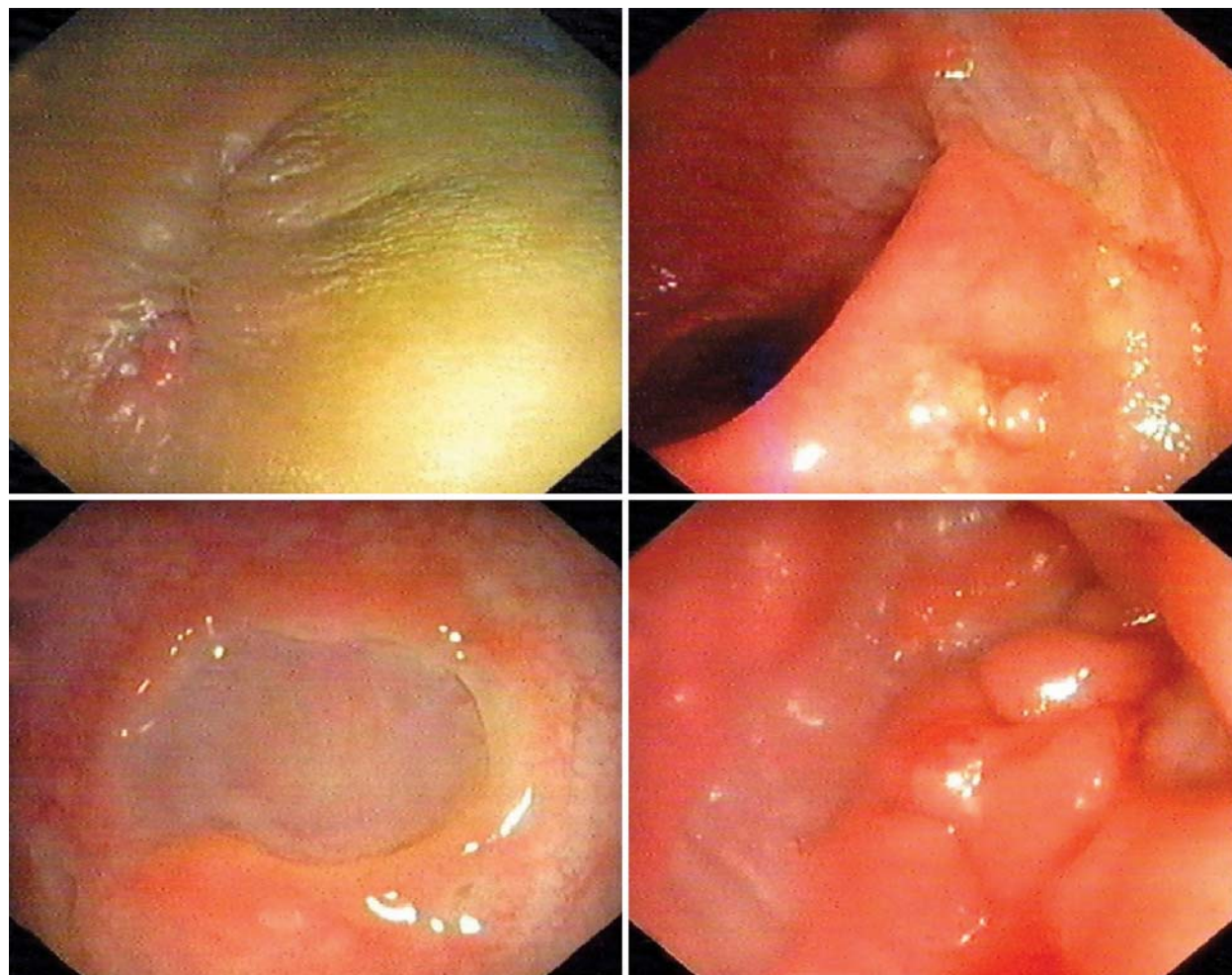


Figure 12 Perianal fistula, colonoscopic picture showing deep fissured and punched out ulcers with cobblestone appearance in case of Crohn's colitis

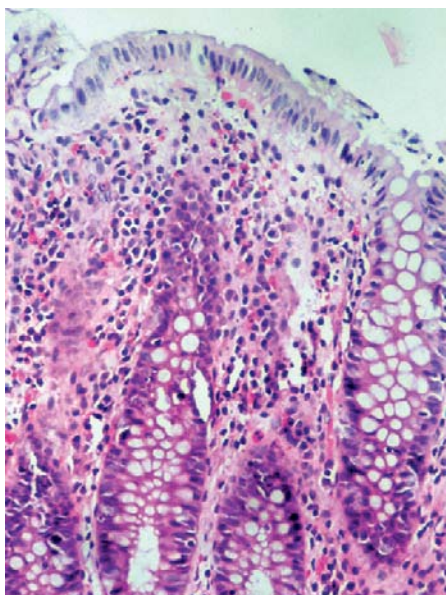


Figure 13A Histopathological picture of colon showing subepithelial thick collagenous band suggestive of collagenous colitis

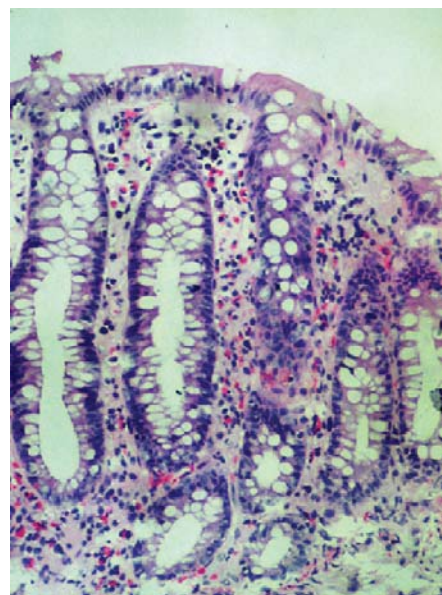


Figure 13B Histopathological picture of colon showing increased intraepithelial lymphocytes in lymphocytic colitis

semi formed stool after awakening. As the day progresses, stools become more watery and smaller in volume. Transit time of enteral contents may be especially short, and parents frequently describe undigested food remnants in the stool. Although some affected children describe mild abdominal discomfort, most typically appear healthy and maintain a normal appetite and activity level. Potential pathophysiology mechanisms for CNSD include increased intestinal motility and osmotic effects of intraluminal solutes (e.g., carbohydrates). The toddlers have great affection for fruit juices and cold beverages. Therefore excessive intake of fruit juices, particularly those containing sorbitol or fructose (e.g., apple, pear, cherry, and prune juices), may contribute to the stool osmotic load, thus causing or worsening diarrhea. Reassurance is the cornerstone of therapy for CNSD. Parents should be assured that their child is growing well and is healthy. Dietary modification, including the avoidance of sucrose and fructose is the main stay of treatment. Beyond the restriction of fruit juices, possible helpful changes may be to liberalize fat to encourage normal caloric intake and to slow intestinal transit time, not to restrict fiber, and to assure adequate but not overhydration. Try to rule out organic causes as far as possible.

Irritable Bowel Syndrome

This is a most common functional disorder of GI tract in older children. This is characterized by pain abdomen followed by act of defecation that relieves the pain. Three types of IBS are associated with diarrhea, constipation or combination of both. The genesis of pain involves complex genetic, psychological and somatic factors. Majority of the times children are suffering from other psychological or functional disorders. Usually the symptomatology is of chronic nature. According to ROME III diagnostic criteria there has to be pain abdomen for 2 months plus 2 or more of the following at least 25% of the time: (1) improvement with defecation, (2) onset associated with change in the frequency of stools, (3) onset associated with change in the form of stool and (4) no evidence of IBD or neoplasia. Elaborate investigations are not needed in this condition. The family history of functional GI disorders is positive in 50–70% of one or both of the parents. The symptoms of diarrhea respond to reassurance and *isabgol* (*Psyllium* seed, *Ispaghula*,

or *Psyllium* spogel) husk. The role of drugs in children is not well defined.

Functional Diarrhea

This is an uncommon but does occur in older children. The factors responsible are similar to those of CNSD. In addition psychological factors and stressors may be there. Try to rule out organic causes. Treatment is reassurance, *isabgol* husk and the measures described under CNSD.

Factitious Diarrhea

It is also known as laxative abuse or Munchausen syndrome by proxy. High index of suspicion to be observed while evaluating the patient for chronic diarrhea and this is one of the condition that is liable to be missed. Patients with other psychiatric conditions like anorexia and bulimia nervosa are more prone than general population. Subtle clues can be identified in investigations such as hypokalemia, which suggests ingestion of stimulants, pseudomelanosis coli in chronic anthracene laxatives such as *senna* or *cascara*. Presence of a large fecal osmotic gap suggests magnesium ingestion. If the suspicion is high, sample should be subjected to laxative analysis in form of spectrophotometer, etc. Treatment is mainly the behavioral therapy and avoidance of laxative.

PREVENTION

Postinfectious chronic diarrhea can be prevented by giving adequate nutrition during an episode of acute diarrhea. Breast-feeding during infancy is protective against GI infections. Avoiding early introduction of animal milk can prevent CMPA. Supplementation of zinc and other micronutrients is also important to prevent prolongation of diarrheal duration and recurrence. Rotavirus vaccine is available to prevent the rotavirus infection in infants and children less than 5 years of age. In developing countries raising the standards of living, hygiene and sanitation are equally important steps to prevent infectious diarrhea. HIV infection can be prevented by following universal precautions. Antenatal diagnosis of some of the congenital conditions is possible. However, noninfectious causes of chronic

diarrhea are difficult to prevent but early recognition, diagnosis and appropriate intervention can avoid complications and ensure better outcome.

PROGNOSIS AND OUTCOME

Prognosis of chronic diarrhea depends upon the underlying etiology. The outcome of persistent diarrhea is determined by the underlying nutritional status and the age of the child. With dietary modification the outcome is good. Severe malnutrition and intractable diarrhea of infancy are associated with high morbidity and mortality. Earlier mortality used to be 40–50% but now with the better understanding of enteral and parenteral nutrition the mortality has significantly come down to 5%. The mortality due to immune deficient states and pancreatic disorders is still very high. The replacement therapy in pancreatic exocrine insufficiency is very difficult to maintain due to high cost of enzyme therapy. Overall prognosis of chronic diarrhea has changed due to better understanding of pathophysiology, etiopathogenesis and newer treatment modalities. The follow-up, monitoring of treatment, assessment of anthropometry and dietary modifications and supplementation of nutrients at regular intervals have a key role to play for better outcome.

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IN A NUTSHELL

1. Type of chronic diarrhea should be well-defined based upon clinical features and the investigations.
2. Common causes of chronic diarrhea are celiac disease, persistent diarrhea, cow milk protein allergy, and giardiasis.
3. Meticulous approach is important to categorize the type of chronic diarrhea (small or large bowel on the basis of characteristics of the stool).
4. Neonatal diarrhea, congenital or acquired is a challenge to manage.
5. Protracted or intractable diarrhea of infancy is different from chronic diarrhea in older children. There is a great impact on the nutrition and growth of infant.
6. Supportive care in form of appropriate, age specific dietary modification and supplementation of vitamins/minerals is mandatory.
7. Etiology of chronic diarrhea must be ascertained before specific therapy.
8. Nonspecific chronic diarrhea in preschool children, functional diarrhea, factitious diarrhea and irritable bowel syndrome should be recognized.
9. The prognosis and outcome depend upon the underlying etiology, complication and effective therapy.
10. Early recognition of etiology of chronic diarrhea and timely intervention can avoid long-term complications.

Chapter 36.6

Antibiotic Associated Diarrhea

Seema Alam, Vikrant Sood

A universal consensus on the definition of antibiotic associated diarrhea (AAD) is still elusive but commonly it is described as frequent, watery stools that occur in response to use of antibiotics to treat infections. Early onset of AAD occurs within 2–7 days, while delayed onset may occur within 2–8 weeks after the antibiotic are discontinued. The definition requires exclusion of other common causes of diarrhea including intercurrent infection such as viral gastroenteritis or bacterial infection, laxative use, or diarrhea from other causes.

EPIDEMIOLOGY

There is scarcity of data on the prevalence of AAD in children worldwide with no Indian studies (**Table 1**). Available data suggest that the prevalence of AAD is 13–29 % in majority of the studies. High prevalence of 59–80% seen in some studies can be explained by their small sample. The only data from Asia is from two studies done in Chinese children revealing a prevalence of 16.8% and 19.4% and a study among 225 Thai children, where 6.2% had AAD when amoxicillin and cloxacillin combination was the most common antibiotic prescribed. There was a trend towards a higher

incidence of AAD in the amoxicillin/clavulanate group (16.7%) compared to amoxicillin (6.9%) and erythromycin (11.1%) groups. Almost all these studies have been done in the developed countries with no comparable data from the developing world.

ETIOLOGY

Mild AAD would present with only watery stools, occur sporadically and resolve on withdrawal of the antibiotic. They are usually *C. difficile* (CD) toxin negative and do not need any further treatment. The most common organism found associated with AAD is CD, though a large majority remains undiagnosed. Other less commonly involved organisms include *Staphylococcus aureus*, *Clostridium perfringens*, *Klebsiella oxytoca* and *Candida*.

Relevance of *Clostridium difficile*

Clostridium difficile is a gram-positive, spore-forming obligate anaerobe, ubiquitous in the environment, and widely distributed in healthcare settings. Spores are ingested via contact with contaminated surfaces and, under favorable conditions (in susceptible hosts), will germinate to a vegetative state that produces toxins. Antibiotic-mediated suppression of normal human gut microbiota is strongly associated with colonization and proliferation of CD. It is the most common cause of AAD with incidence varying from 10% to 20% of all cases of AAD, and almost all cases of colitis associated with antibiotic therapy. Initial data suggested increase in CD infection paralleling the widespread epidemic of irrational antibiotic use. As seen in the **Table 2**, at least three studies

Table 1 Prevalence of antibiotic associated diarrhea (AAD) in children

Author	Place	Study type	Prevalence of AAD (%)	Age group	All or particular antibiotics	Outpatient or hospitalized patients
Mitchell 1996	USA	Prevalence	22/76 (28.9%)	12–47 months	Amox/clav	Outpatient
Vanderhoof 1999	USA	RCT	25/95 (26%)	6 months–10 years	All	Outpatients
Arvola 1999	Finland	RCT	9/58 (16%)	0–12 years	Amoxicillin	Outpatient
Jirapinyo 2002	Thailand	CT	8/ 10 (80%)	1–36 months	All	Hospitalized
Turkey 2003	USA	Prevalence	71/650 (11%)	1 month–15.4 years	All	Outpatients
La Rosa 2003	Italy	CT	31/50 (62%)	6.6 years	All	Outpatients
Sekhi H 2003	Japan	CT	16/27 (59%)	---	All	Outpatients
Kotowska 2005	Poland	RCT	22/127 (17.3%)	5 months–15 years	All	Outpatient and hospitalized
Ruszczynski 2008	Poland	RCT	20/120 (17%)	3 months–14 years	All	Outpatients and hospitalized
Shan 2013	China	RCT	28/144 (19.4%)	6 months–14 years	All	Hospitalized
Gaiazzi 2013	Italy	Prevalence	42/322 (13 %)	1–8 years	All	Outpatient
Zheng YJ 2012	China	RCT	30/179 (16.8%)	3 months–3 years	All	Hospitalized

Abbreviations: RCT, randomized controlled trials; CT, controlled trials.

Table 2 Incidence of *Clostridium difficile* associated diarrhea (CDAD)

Study	Subjects (n)	Age	Time period	Incidence of CDAD
Kim et al.	4,895	< 18 years	2001–2006	4.4–6.5 per 10,000 patient-days
Nylund et al.	21,274	1–18 years	1997–2006	3,565–7,779
Zilberberg et al.	-	< 18 years	1997–2006	7.24–12.80/10,000 hospitalizations
Schwartz et al.	299	1–17 years	2008–2012	8.3/10,000 patient days*

*Yearly incidence static over study time period.

have found an increase in the incidence of *Clostridium difficile* associated diarrhea (CDAD) in the children in the last decade. But a cohort of 299 hospitalized children (1–17 years of age) with CD infection at a large tertiary care center, the incidence rate of CD infection (8.3 cases per 10,000 patient days) did not change significantly over the 4 year study period.

Adult data from Indian population reports a prevalence varying from 7% to 17% in hospitalized diarrheal cases (**Table 3**). In contradiction to Western data, a retrospective chart review at an Indian tertiary care hospital reported 524 cases over a 5-year period of which 7.1% specimens were positive for CD toxin with decreasing yearly incidence throughout the stay (11.2% in 2001, 9.4% in 2002, 8.6% in 2003, 5% in 2004 and 4% in 2005). This may be due to stringent surveillance and an improved antibiotic policy followed at the tertiary care hospital. Indian pediatric data on CD infection presents a similar picture.

Table 3 Prevalence of *Clostridium difficile* associated diarrhea (CDAD) in Indian population

Author Year	Number of Subjects	Prevalence of CDAD (%)	Out/Inpatient
Niyogi 1991	341 diarrheal cases 172 controls	11.1 3	Inpatient
Bhattacharya 1991	233	7.3	Inpatient
Dhawan 1999	210	15	Inpatient
Chaudhry 2008	524	7.1	Inpatient
Joshya 2009	214	12.1	Inpatient
Ingle 2011	99	17	Inpatient
Kaneria 2012	50 diarrheal cases 50 controls	10 6	Inpatient

The incidence of CD increased significantly in the outpatient setting, particularly in the emergency department (1.18 cases vs. 2.47 cases per 1,000 visits). The incidence among inpatients decreased during the study period (1.024 cases vs. 0.680 cases per 1,000 patient-days). These studies suggest that the incidence of community acquired CD infection is also increasing in the pediatric population. Some cases of CD infection can be expected to occur in the weeks or even months following discharge. In addition, the increased circulation of CD within hospitals will increase the rate of asymptomatic CD carriers within the population. Contact with such cases will in the end lead to some cases of community acquired CD infection. Furthermore, it has been suggested that an animal reservoir may play a role in the emergence of community-acquired CD infection. The pediatricians need to keep this in mind while treating difficult diarrhea in the hospital and the community. Comparable Indian data is not available.

RISK FACTORS FOR ANTIBIOTIC ASSOCIATED DIARRHEA

Type of Antibiotic Used

The antibiotics with which AAD is associated are: penicillin G and V (3%), penicillin A and M (11%), amoxicillin-clavulanate (23%), cephalosporins (9%), macrolides (8%), trimethoprim-sulfamethoxazole (6%) and erythromycin (16%). Statistically significant difference is seen between the rates of onset of AAD with amoxicillin/clavulanate compared with all other antibiotics combined. Higher prevalence was found in those where amoxy-

clavulanate was the only antibiotic used. The relative risk (RR) of diarrhea was between 3 and 5 for penicillin V, amoxicillin, and nystatin; 6.5 for a first-generation cephalosporin; and 10.2 for cloxacillin has been reported by Kramer et al., although the author did not define AAD. The rate of AAD associated with parenterally administered antibiotics especially those with enterohepatic circulation was similar to rates associated with oral antibiotics.

Age

In some studies the younger children of less than 2 years were more often associated with AAD. The highest incidence (18%) of AAD was in the 2 months to 2 years age group. Among adults, it is elderly who are more likely to have AAD. So the extremes of age have a higher risk of developing AAD. The RR of onset of an episode of diarrhea in a child receiving amoxicillin/clavulanate was 2.43 (range, 1.4–4.21) and 3.5 (1.89–6.46) when the child was aged less than 2 years.

Hospitalization

Lower rates of AAD in outpatients compared to hospitalized ones is based on their better health status and lack of exposure to highly virulent nosocomial pathogens.

Comorbidity

Incidence of AAD varies widely being influenced by underlying comorbid illnesses, use of acid suppressing medications, duration of hospitalization, prolonged nasogastric tube insertion, gastrostomy and jejunostomy tubes, underlying bowel disease, gastrointestinal tract surgery, and impaired humoral immunity.

Risk Factors for *Clostridium difficile*-associated Diarrhea

Antibiotic usage, though not the only prerequisite, remains the most important risk factor for occurrence of CDAD, which is highly modifiable. Most commonly implicated ones include ampicillin (or amoxicillin), clindamycin, cephalosporins (in particular the third generation cephalosporins such as cefotaxime, ceftriaxone and ceftazidime) and quinolones, though all antibiotics, even vancomycin and metronidazole on rare occasion, have been reported to cause CDAD. Change from cefotaxime to ceftriaxone for initial treatment of severe sepsis or pneumonia in medical patients led to the average number of patients with CD toxin-positive stools per quarter to increase from 16 to 39 but further shift to levofloxacin helped in bringing it down to five cases a year later in an Irish hospital. The delay in the decline of CDAD after virtual withdrawal of cephalosporins may reflect a slowly diminishing environmental reservoir. Decrease in intravenous (IV) cephalosporins usage from 210 to 28 defined daily doses with corresponding increase in piperacillin-tazobactam and moxifloxacin ($p < 0.001$) led to significant decrease in the relative risk (RR 3.24, 95%CI 1.07–9.84, $p = 0.03$) of developing *Clostridium difficile* infection.

Use of rectal thermometers and polyvinyl gloves and environmental contamination are the other risk factors for CDAD.

PATHOGENESIS

Commensal microbes resist colonization of pathogens via various mechanisms including competition for nutrients, production of pathogen inhibiting substances and competitive inhibition of pathogen binding/toxin receptor sites. Disruption of normal enteric flora caused by the antibiotic usage may lead to overgrowth of pathogens secondary to decrease in colonization resistance. Functional disturbances of the intestinal carbohydrates (secondary

to lack of colonic digestion of complex carbohydrates and absence of absorption promoting short chain fatty acids) and bile acids metabolism results in osmotic diarrhea. Also, use of other drugs might affect the intestinal mucosa and the motility. Erythromycin accelerates the rate of gastric emptying; amoxicillin-clavulanate stimulates small bowel motility.

CLINICAL PRESENTATION

More than two-thirds of the children develop AAD during the antibiotic therapy and 15% in the week following after stopping antibiotic. 17% present during antibiotic treatment and continue after stopping the antibiotic. AAD was seen to begin 5.3 ± 3.5 days after start of antibiotic and the mean duration was 4 ± 3 days with none requiring hospitalization. In some studies the younger children of less than 2 years were more often associated with AAD. High prevalence of AAD was seen in the studies not using the standard definition of AAD. Most of them have reported mild illness.

Symptomatology in CDAD ranges from asymptomatic colonization (37% for infants 0–1 month of age, 30% between 1 month and 6 months of age, 14% between 6 months and 12 months of age, and adult rate of 0–3% by 3 years of age) or minor symptoms as acute gastroenteritis (in younger children) to more profound diseased states like pseudomembranous colitis. Pseudomembranous colitis usually presents with abdominal cramps, fever, leukocytosis, fecal leukocytes, hypoalbuminemia, colonic thickening on computed tomography (CT) scan and widely spread punctate yellow plaques on endoscopic examination. This form of colitis follows administration of clindamycin, cephalosporins and penicillin, occurring as an epidemic or endemic in a hospital with usually no previous history of antibiotic intolerance. Most of these cases are CD toxin positive. These may result in increased morbidity and mortality as evident by a 2–3-fold increase in length of hospital stay, a 6-fold increase in the risk of mortality, and the need for colectomy (approximately 2%). Children may have a better outcome with CDAD as depicted in a recent study by Schwartz et al. In this study, 90% of children with CDAD experienced resolution of symptoms by 30 days after disease onset and only 2% experienced a severe outcome. CDAD have a symptomatic recurrence of 15–35%. This is a serious problem since they increase length and overall cost of hospitalization. The longer hospitalization is also responsible for reinfection due to a different strain from the hospital environment.

DIAGNOSIS

Differential diagnosis of AAD includes acute infective diarrhea—viral or bacterial pathogens; mucosal diseases—inflammatory bowel diseases, short bowel syndrome etc.; food allergy, and other medications associated diarrhea. Severe diarrhea, liquid stool with mucus and blood, fecal leukocytes more than 5/high power field, altered flora and presence of gram-positive bacilli with oval subterminal spores are sensitive predictors for diagnosis of CD infection. The cytotoxin assay that uses tissue culture is the gold standard for diagnosis. It is very sensitive test detecting as little as 10 pg of toxin B.

The enzyme-linked immunosorbent assay (ELISA) available for detection of CD has a false negative rate of 10–20% since about 100–1,000 pg of the toxin A and B are needed for the test to be positive. Few of the strains just produce toxin B so the test which detect both toxin A and B should be preferred. ELISA is more easily available, results are available within hours and the cost is about \$40 per test. Therefore, detection of toxin A and B by ELISA and detection of toxin B by tissue culture form the mainstay in the diagnosis of CD.

Stool culture is not easily available but has high sensitivity with low specificity. CD was isolated on culture from stool specimen of 16/80 (20%) patients, while 23 (28.8%) stool specimens were positive for CD toxin. CD has been isolated in 7.2% by culture whereas the overall positivity was 18% by ELISA. Diagnosis of CD by culture is difficult and time consuming because of strict anaerobic nature of organism. Moreover, mere isolation of CD on culture is not sufficient to establish the pathogenic role of these isolates. ELISA for the detection of toxin A and B is recommended to ensure rapid diagnosis of CD. A two-step algorithm evaluated in 1,468 stool specimens first screened the specimens by an immunoassay for CD glutamate dehydrogenase antigen (C.DIFF CHEK-60). Later screen-positive specimens underwent toxin testing by a rapid toxin A/B assay (TOX A/B QUIK CHEK); toxin-negative specimens were subjected to stool culture. This algorithm allowed final results for 92% of specimens with a turnaround time of 4 hours.

TREATMENT

The management options for AAD include discontinuation of implicated antibiotics and use of supportive management with fluid and electrolytes if required. Avoidance of usage of any antiperistaltic drug (may precipitate toxic megacolon) and control of infection in the patient with other antibiotics are also important. In some of cases of CDAD, withdrawal of the inciting agent will lead to resolution of clinical signs in three days. Oral metronidazole or oral vancomycin (for a duration of 10 days) are the drugs of choice for CDAD with more than 90% cure rates for both. Using metronidazole allows the treatment cost to be low and also prevents the development of vancomycin-resistant enterococci. Vancomycin should be reserved for those with severe illness, or intolerance or failure to metronidazole. Treatment regimens may also include probiotics, bile-acid sequestrants and IV immunoglobulin (IVIG). Most recurrences also respond to this line of management. A prolonged treatment with low dose vancomycin is preferred for the repeated recurrences. Metronidazole, in view of low cost and established efficacy, is the drug of choice for the initial treatment with mild to moderate disease while reserving oral vancomycin with or without IV metronidazole for patients with severe disease and for patients who do not respond to oral metronidazole. To reduce the costs, use of IV formulation compounded by pharmacy into oral solution can be used to the best advantage.

Use of gloves with symptomatic patients, washing of hands with soap and water, and environmental decontamination are key control measures. Latest treatment modalities include newer antibiotics (rifaximin, nitazoxanide and fidaxomicin), fecal microbiota transplantation, and various experimental options (rifalazil, ramaplanin, tolevamer, monoclonal antibodies).

PREVENTION

Handwashing, isolation and environmental decontamination are the factors which can prevent recurrences and reinfection. Avoidance of usage of rectal thermometers, usage of vinyl gloves and hospital antibiotic policies are other factors which can help.

Role of Probiotics

Probiotics are living microorganisms, which when administered in adequate amounts that confer a health benefit to the host. Antibiotics disrupt the natural microbial flora of the intestine leading to overgrowth of pathogens while decreasing the colonization resistance. Probiotics, thereby acting as surrogate normal flora, act to protect the intestine until the normal microbiota can recover. Other potential mechanisms of action

include production of bacteriocins, stimulation of the immune response, production of toxin-destroying proteases, attachment site interference, etc.

Saccharomyces boulardii and *Lactobacillus spp.* (e.g., *Lactobacillus rhamnosus GG*) are the most popular species used as probiotics with documented benefit in various trials. *S. boulardii* has been shown to prevent the binding of toxin A to inactivate toxins A and B by proteolytic digestion, inhibition of CD adhesion, cellular protection from histologic damage and inhibition of proinflammatory cytokine gene expression.

A recent Cochrane analysis (23 trials, 4,213 participants) to assess the efficacy and safety of probiotics for preventing CDAD or CD infection in adults and children, suggested that probiotics significantly reduce this risk by 64%. The incidence of CDAD was 2.0% in the probiotic group compared to 5.5% in the placebo or no treatment control group (RR 0.36; 95% CI 0.26–0.51). The incidence of CD infection was 12.6% in the probiotics group compared to 12.7% in the placebo or no treatment control group. In another meta-analysis to assess the efficacy and safety of probiotics for preventing pediatric AAD (22 trials, 23 treatment arms and 4,155 participants) and CD infections (5 trials, 1,211 participants), probiotics (all strains combined) significantly reduced the incidence of pediatric AAD (pooled RR = 0.42, 95% CI: 0.33–0.53) and significantly reduced pediatric CD infection (pooled RR = 0.35, 95% CI: 0.13–0.92). Both *Saccharomyces boulardii lyo* and *Lactobacillus rhamnosus GG* significantly reduced pediatric AAD. There was no significant effect by type of antibiotic, or by duration or dose of probiotic. No adverse events were found relating to the use of probiotics. Thus, it concluded that probiotics significantly prevented pediatric antibiotic associated diarrhea and pediatric CD infection.

Risk benefit ratio needs to be carefully balanced while using probiotics (especially *S. boulardii*) in select group of patients. These include those with intravascular catheters and critically ill debilitated immunocompromised patients. The risks include increased chances of fungemia with probiotics as a probable source. It is important to note here that we need to now concentrate on specific probiotics individually when assessing their role in AAD or in other disorders, because clubbing together the effective strains with ineffective ones might actually be diluting the effect of the former. These meta-analyses raise the issue of how cost-effective is the addition of probiotics to antibiotics in the developing world. Probiotics may have a potential role to play in the prevention of AAD but the cost benefit ratio should be carefully assessed. Since the prevalence of AAD is low and the addition of probiotics is going to prevent only 1 in 7–10 cases of AAD, it may not be very cost-effective to routinely add probiotics to antibiotics in children.

IN A NUTSHELL

1. Prevalence of antibiotic associated diarrhea (AAD) is around 11% in children receiving antibiotics.
2. Children younger than 2 years and type of antibiotics are the two risk factors identified for AAD.
3. The most common organism found associated with AAD is *Clostridium difficile*; other less commonly involved organisms include *Staphylococcus aureus*, *Clostridium perfringens*, *Klebsiella oxytoca* and *Candida*.
4. The incidence of community acquired *Clostridium difficile* is increasing in the pediatric population.
5. Detection of toxin A and B by ELISA and detection of toxin B by tissue culture form the mainstay in the diagnosis of *C. difficile*. There should be a two-step method to detect CD infection.
6. Most of the AAD would respond to only discontinuation or change of the antibiotic. Oral metronidazole or oral vancomycin are drugs of choice for *Clostridium difficile*.
7. Probiotics reduce the risk of AAD in children, when given to 7–10 patients along with antibiotics would prevent AAD in one child.
8. Cochrane analysis confirms the efficacy (reduce this risk by 64%) and safety of probiotics for preventing CDAD or CD infection in adults and children.

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Section 37 HEPATOBILIARY DISEASES

Section Editor Surender Kumar Yachha

Chapter 37.1

Applied Anatomy and Physiology of Liver and Biliary Tract

Vishnu Biradar

It is important to have basic knowledge of anatomy, physiology and histology of the liver to understand its diseases and their complications. This chapter discusses in a brief about development of the liver followed by normal anatomy and histology of the liver and lastly physiologic functions of liver.

DEVELOPMENT OF LIVER

Liver is developed in fetus in the 3rd–4th week of gestation from two primordial buds. Hepatic outgrowth from foregut endoderm develops into the parenchyma and septum transversum develops into the connective tissue elements of the hepatic stroma and capsule. Septum transversum is invaded by cranial part of diverticulum. Furthermore, cranial part of diverticulum forms the prehepatocytes or hepatoblasts inside the septum transversum, and is organized in cords around developing sinusoids derived from branches of the vitelline veins that penetrate the septum transversum. The caudal part of the hepatic diverticulum forms the extrahepatic biliary tree and ventral pancreatic anlage. The extrahepatic biliary tree is recognizable in 4-week-old embryo. Rest of the biliary tract structures such as gallbladder, cystic duct, hepatic ducts, common bile ducts and pancreatic duct are visible by end of 5 weeks. By 16th week, biliary duct system is fully formed.

Secretion of factors such as bone morphogenic protein (BMP) by the mesenchymal cells of the septum transversum and of fibroblast growth factors (FGF) by the precardiac mesoderm appear to play an important role in the induction of hepatogenesis. The development of the liver is also associated with changes in the vitelline veins and in the umbilical veins. Venous system is recognizable in 7-week-old embryo. The development of the intrahepatic biliary tree begins between the 5th and 9th week postfertilization. Biliary epithelium is believed to arise from precursor bipotential hepatoblasts that can differentiate into either hepatocytes or biliary epithelial cells. *HNF-1 β* and *HNF-6* genes or gene products regularize this process. The Notch pathway is also involved in bile duct development; the Jagged1/Notch2 interaction may be critical for induction of biliary differentiation and repression of hepatocytic differentiations. The liver becomes the site of hematopoiesis between 6 and 7 weeks. As the fetus enters the third trimester, hematopoiesis diminishes and becomes focal. Little hematopoiesis is seen in portal tract after 32 weeks of gestation.

Embryological changes in liver development are outlined in

Table 1 Hepatic development

Developmental age	Characteristic
Week 3–4	Hepatic diverticulum appears as an evagination of the foregut
Week 5	Umbilical veins connect with the developing hepatic sinusoids. Ductal plate begins to form hematopoiesis
Week 6	Hematopoiesis begins
Week 7	Definitive venous pattern established within the liver
Week 9	Liver accounts for 10% of fetal weight
Week 12	Remodeling of the ductal plate. Bile formation begins
Week 16	Major bile ducts formed at porta hepatis
Week 36	Hematopoiesis reduced to small widely spaced islands

ANATOMY

Liver is the largest solid organ in our body, situated just below the right diaphragm and divided by falciform ligament anteriorly into right and left lobes. Parietal peritoneum covers the liver except for the bare area, where the liver remains in direct contact with the diaphragm and is suspended by fibrous tissue and the hepatic veins. It is attached to diaphragm by the superior and inferior coronary ligaments and the right and left triangular ligaments. Inferiorly, there are two distinct lobes: (1) caudate and (2) quadrate lobes. The caudate lobe has boundaries of the inferior vena cava groove, porta hepatis and ligamentum venosum fissure. On the inferior surface, the quadrate lobe is defined by the gallbladder fossa, porta hepatis and ligamentum teres hepatis. The true right and left lobes of the liver are roughly equal size and are not divided by the falciform ligament, but by a plane passing through the bed of gallbladder and the notch of the inferior vena cava. *Liver is divided into eight segments by Claude Couinaud on basis of distribution of portal and hepatic veins.* Couinaud lobes were numbered in clockwise fashion from 1 to 8 starting from caudate lobe being segment 1. Segments 1 to 4 form left lobe and segments 5–8 form the right lobe.

Approximately 70% of blood is supplied to liver from the portal vein and rest 30% from the hepatic artery. The portal vein is formed behind the neck of pancreas by the superior mesenteric vein and the splenic vein. At the hilum, the portal vein divides into right and left branches. The hepatic artery commonly arises from the celiac trunk. Within the hilum, portal vein is posterior to the hepatic artery and hepatic artery is on the right side of the bile duct. In the liver parenchyma, the arteries, portal veins, and bile ducts are surrounded by a fibrous sheath, the Glissonian sheath, whereas the hepatic veins lack this structure. Majority of the venous drainage of the liver is accomplished by three major hepatic veins: (1) right, (2) middle and (3) left drains into the inferior vena cava, except that the caudate lobe drains into inferior vena cava directly.

Table 1.

Each lobe is drained by right and left hepatic ducts, which joins to form the common bile duct. The cystic duct usually drains into the lateral aspect of the common hepatic duct. The caudate lobe drains into the left hepatic ducts. The liver is innervated by both sympathetic and parasympathetic nerve fibres. Lymphatic drainage of liver surface occurs to the nearest lymph nodes.

FUNCTIONAL UNITS AND HISTOLOGY

Under the low power (10 X) microscope, normal liver consists of a regular structure based on portal tracts and efferent veins. A typical *portal tract* contains portal venules, hepatic arterioles and small interlobular bile ducts (**Fig. 1**). Blood from both venules and arterioles pass through the sinusoidal system to reach efferent hepatic venules. From these, the blood drains into successively larger veins to reach the inferior vena cava. Bile is secreted into bile canaliculi, which flows towards canals of Hering and to the bile ductules and hence to interlobular bile ducts, further from the smallest ducts into larger ducts, to reach the small intestine by the way of common bile duct.

The functional relationship between these various structures has been the subject of much debate. The most widely used models are the Kiernan's classic lobule and Rappaport's acinus. The Kiernan's classic lobule has an efferent venule at its center and portal tracts at its periphery, hexagonal unit (**Fig. 2**). The Rappaport's acinus is 3D structure, based on a terminal portal tract, with blood passing from this, through successively less well-oxygenated parenchymal zones 1, 2 and 3, to efferent venules. It is worth emphasizing that both lobules and acini are concepts rather than fixed anatomical structures. Both these concepts have their merits in different situations. For example, the sinusoidal congestion of venous outflow obstruction is often more easily understood on the basis of the lobule, with maximum intensity at its center. Bridging hepatic necrosis, however, is difficult to understand in terms of the lobule and has been explained as death of hepatocytes in acinar zone 3, the zones in which oxygen saturation is relatively low.

The hepatocytes are arranged in plates separated by the sinusoidal labyrinth. The layer of hepatocytes next to a small portal tract is known as the limiting plate, which is one celled. In children, limiting plate may be two cells thick. Hepatocytes are polygonal cells with well-defined cell borders. Most cells contain one diploid nucleus. Nucleoli are often visible, with rare mitotic figures. Polyploidy and variation in nuclear size is therefore normal

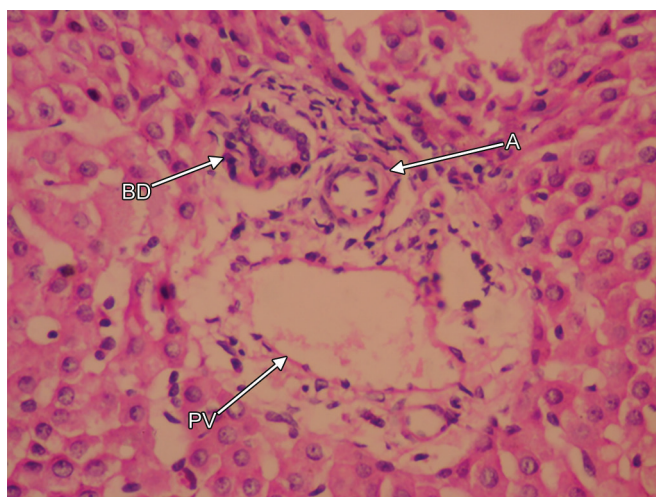


Figure 1 Normal portal tract

Abbreviations: BD, bile duct; A, arteriole; PV, portal vein branch.
Source: Dr Vijayshri Bhide.



Figure 2 Classic hepatic lobule

Abbreviations: CV, central venule, PT, portal tract.

Source: Dr Vijayshri Bhide.

characteristics of human liver. A few nuclei may appear vacuolated because of glycogen accumulation, especially in children and adolescents. Hepatocyte cytoplasm is normally rich in glycogen. Many different proteins such as albumin can be demonstrated in or on the hepatocytes, in keeping with the several metabolic functions of liver. Between the hepatocytes, their walls formed by two or three cells, are the bile canaliculi. Lipofuscin is a normal constituent of adult liver, increasing in amount with age, but also sometimes found in children.

Sinusoidal endothelial cells form a continuous lining which is fenestrated, allowing passage of macromolecules between sinusoids and the space of Disse, which separates the hepatocytes and the space of Disse. Perisinusoidal cells, or cells of Ito, are stellate-shaped fat-storing cells lying between hepatocytes and the space of Disse. They store vitamin A and appear to play a significant role in fibrogenesis. Kupffer cells lie on the sinusoidal surface. They are part of the reticuloendothelial system, and their main function is phagocytosis.

BIOPSY OF THE NORMAL LIVER

Percutaneous liver biopsies are necessarily taken through the liver capsule, which may be seen at one of the core or as a separate piece. Minimum 6 g of liver tissue is considered as adequate and must contain at least six portal tracts. For enzyme analysis, 30 g tissue is required. For copper estimation, 1–2 g of liver tissue is sufficient. Transjugular biopsy specimen may be small and fragmented, especially in patients with cirrhosis, but are usually adequate for histological diagnosis.

Surgical biopsies taken from the inferior margin of the liver are in the form of wedges covered on two aspects by capsule. The structure of the immediately subcapsular zone differs somewhat from the deeper tissue, but there is good correlation between the volume fraction if nonparenchymal components in subcapsular and deeper zone. The appearances mimicking cirrhosis do not usually extend beyond 2 mm into the liver, and confusion is unlikely except with very small samples. In surgical biopsies taken some time after the beginning of an operation, neutrophil leukocytes accumulate under the capsule and in portal tracts, around terminal venules and focally within the parenchyma. Here, there is focal loss of hepatocytes. Similar parenchymal changes have been reported after heavy sedation without full anesthesia. They may also found in patients infected with cytomegalovirus.

Normal Appearances in Childhood

Hematopoiesis in liver is active during the fetal period and continues until a few weeks after birth. Hematopoietic cells are present in portal tracts and sinusoids. Hepatocyte plates are mainly two cells thick until the age of 5 or 6, when the adult pattern of single cell plates is established. Hepatocytes and their nuclei may vary in size. Glycogen vacuolation of nuclei is common in adolescents. Lipofuscin pigment is absent or scanty in the first two decades of life.

LIVER PHYSIOLOGY AND METABOLISM

There are numerous pathways for metabolism of carbohydrate, protein, fat and other substances present in hepatocytes. They are regulated by various hormones secreted by endocrine tissues. Metabolic changes occurring during development of liver are listed in **Box 1**.

BOX 1 Metabolic changes during liver development

- Accumulation of glycogen in fetal liver (to levels two- to three-fold higher than in the adult by term)
- Low rates of gluconeogenesis by fetal liver
- Low rates of glucose use by fetal liver
- Amino acids an important energy source for fetal liver (extensive transamination and oxidative degradation)
- High capacity of fetal liver for fatty acid synthesis
- Rapid induction of ability to oxidize fatty acids during first day of life
- Fatty acid oxidation critical to support of hepatic gluconeogenesis
- Rapid increase in hepatic ketogenesis after birth.

Bile Metabolism

Hemoglobin from senescent red blood cells (RBCs) is broken down to heme and protein. Heme is then converted into bilirubin, which is unconjugated and in insoluble form. One gram of hemoglobin produces 34 mg of bilirubin. This unconjugated bilirubin binds to albumin by noncovalent bond and is then transported to liver. Albumin bound unconjugated bilirubin gets dissociated, just before uptake by hepatocytes. Unconjugated bilirubin, insoluble form, is taken up by hepatocytes, gets converted by enzyme uridine-5'-diphosphate (UDP) glucuronyl transferase enzyme to soluble form, bilirubin mono- or diglucuronide conjugates which is excreted into canaliculi by canalicular protein multiple drug resistant protein 2 (MRP 2) against concentration gradient (energy dependent). From canaliculi, conjugated bilirubin is excreted into intestine via bile duct system. In intestine, bilirubin is broken down to stercobilirubin which is excreted into feces and urobilinogen which is reabsorbed by intestine. This reabsorbed urobilinogen either gets excreted into urine or recycled by the liver.

Carbohydrate Metabolism

Glucose is required as an energy source, especially for the brain, RBCs, muscle and kidney. Glucose homeostasis is monitored by gut-brain-liver axis. Glucose levels are maintained mainly by the liver. Glucose when in excess gets stored as glycogen in hepatocytes and glycogen gets degraded to glucose during fasting stage. Gluconeogenesis also play important role in forming glucose during fasting. In prolonged fasting, brain utilizes ketones as an energy store. During this, glucose is synthesized by anaerobic glycolysis, i.e., Embden-Meyerhof pathway which forms pyruvate and lactate predominantly by RBCs and from amino acid precursors such as alanine from muscle. Lactose and galactose present abundantly in diet gets absorbed in intestine and enters into metabolic pathway to form either glucose or fat depending on need.

In fetal life, glycogen synthesis starts around 9 weeks of gestation, which increases before birth. After birth, this glycogen is metabolized to glucose preventing hypoglycemia in full term neonate.

Protein Metabolism

Liver synthesizes albumin and other secretory serum proteins. Albumin production starts in utero around 8 weeks of gestation and reaches adult levels in second part of infancy. Liver also produces fibrinogen, transferrin and apolipoproteins and clotting factors.

Fat Metabolism

Fat metabolism occurs by fatty acid oxidation where it produces free fatty acids (FFAs). Fatty acid oxidation occurs in mitochondria and peroxisomes. FFA utilized for gluconeogenesis for energy production when needed. During prolonged fasting, ketones are produced by beta oxidation of fatty acids in mitochondria present in hepatocytes which is utilized by brain for energy. As was mentioned earlier, excess glucose gets converted to glycogen in liver and fat in peripheral tissue, which is deposited in adipose tissue and as a triglyceride in hepatocytes.

Drug Metabolism

Hepatocytes contains various microsomal enzymes like CYP 450 or UDP-glucuronosyltransferase, sulfotransferases, GSTs (dimeric enzymes conjugating glutathione), etc. Newborn liver has low activities of certain enzymes which make it vulnerable to drug toxicity. It is also due to less concentration of antioxidants. Microsomal activities increase in next 1 year after birth, irrespective of gestation of newborn at the time of birth.

IN A NUTSHELL

1. Liver is the largest solid organ, situated below right diaphragm subdivided into eight segments by Couinaud. It is supplied majorly by portal vein blood 70% and by hepatic veins 30%.
2. Liver develops from foregut endoderm with the interplay of factors such as *BMP*, *FGF*, *HNF-1 β* and *HNF-6* genes or gene products, the Jagged1/Notch2 interaction pathway, etc.
3. Functional unit is Rappaport acinus and Kremer's classic lobule which are concepts rather than fixed anatomical structure.
4. Liver biopsy in early infancy may show active hematopoiesis, glycogen vacuolation of nuclei, high content of glycogen, two cell thick hepatocytes plates and absence of lipofuscin which is contrary to adult.
5. Bile acid synthesis and bile excretion is unique feature of liver along with many metabolic pathways of carbohydrate, protein and fat which work simultaneously to meet metabolic demands of body and also drug metabolism.

MORE ON THIS TOPIC

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Chapter 37.2

Liver Function Tests

Neelam Mohan, Sakshi Karkra

Liver is a unique organ which performs synthetic, biochemical and excretory functions, so no single biochemical test can detect the global functions of liver. The title *liver function tests* is, however, somewhat of a misnomer as only the bilirubin and albumin offer information regarding the functional capacity of the liver. Though they lack sensitivity and specificity a good interpretation of these assays do give a lot of information in association with the clinical history, physical examination, radiological imaging and liver biopsy. Advantages and limitations of liver function tests are listed in **Box 1**. Liver functions tests are classified in four categories: i.e., test for (1) Transport of organic anions and metabolism of drugs; (2) Injury to hepatocytes (serum enzyme tests); (3) Biosynthetic capacity; and (4) Clearance of substance from plasma by the liver.

BOX 1 Advantages and limitations of liver function tests

Advantages

- Sensitive screening modality for liver dysfunction
- Useful to recognize the pattern of liver disease, like in differentiating acute viral hepatitis, chronic liver disease (CLD) and various cholestatic disorders
- To assess the severity of liver disease and predict outcome
- For follow-up of patients and in evaluating response to therapy of certain liver diseases like autoimmune liver disease, postliver transplant, etc.

Limitations

- Lack sensitivity and they may be normal in certain liver diseases like congenital hepatic fibrosis, noncirrhotic portal fibrosis and rarely in cirrhosis
- They lack specificity for any particular disease
- Serum albumin may be decreased in CLD but they may be also abnormal in malabsorption, malnutrition, or renal disorders like nephrotic syndrome
- Aminotransferases though done for screening of liver diseases; may be raised in cardiac and muscular diseases
- Liver function tests except for serum bile acids are not specific for liver diseases

TESTS FOR TRANSPORT AND DRUG METABOLISM

Serum Bilirubin

Bilirubin is derived from hemoglobin degradation. Original van D Bergh's method of measuring bilirubin classified bilirubin into direct and indirect. Measurements of bilirubin can be altered by exposure to light, therefore, samples must be kept in dark.

Total bilirubin Normal range is 0.2–0.9 mg/dL (2–15 μ mol/L). It is slightly lower in females as compared to males (by 3–4 μ mol/L).

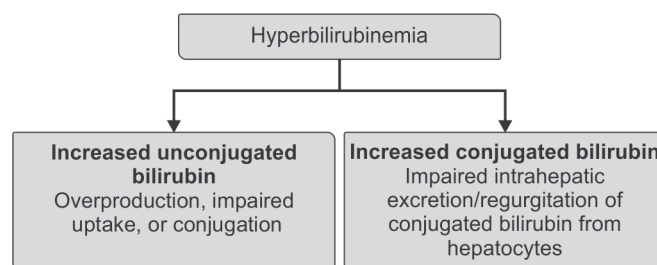
Direct bilirubin This is the water-soluble fraction of the total bilirubin. Normal range is 0.3 mg/dL (5.1 μ mol/L).

Indirect bilirubin This is a measure of unconjugated fraction of bilirubin and is calculated by the difference of the total and direct bilirubin (**Flow chart 1**).

Urine Bilirubin

Unconjugated bilirubin is tightly bound to albumin and not filtered by the glomerulus and thus not present in urine while conjugated bilirubin is water soluble and may be found in urine. In early

Flow chart 1 Types of hyperbilirubinemia



hepatobiliary disease like in acute hepatitis, urine bilirubin may be positive (tests strips impregnated with diazo reagent can detect as little as 0.1–0.2 mg/dL of bilirubin) while the patient may not appear clinically icteric.

Urobilinogen

When the bilirubin glucuronides are secreted into the upper small intestine they are hydrolyzed to unconjugated bilirubin. This is further reduced by the anaerobic intestinal microbial flora to form three colorless tetrapyrroles called urobilinogen. The urobilinogen oxidizes spontaneously to produce the major color pigments of stool in the lower intestinal tract. Around 20% of the urobilinogen produced daily undergo enterohepatic recirculation, majority being taken up by the liver and then re-excreted into bile with a small fraction being excreted in the urine. In biliary obstruction, urine as well as stool urobilinogen excretion decrease to very low concentrations because very small amount of bilirubin reaches the intestinal tract. In patients with hepatocellular dysfunction like viral hepatitis or well-compensated cirrhosis in children, more urobilinogen escapes hepatic uptake and thus appears in the urine.

TESTS FOR HEPATOCYTE INJURY

Enzymes that Detect Hepatocellular Necrosis:

Aminotransferases

The aminotransferases or transaminases are the most frequently utilized and specific indicators of hepatocellular damage. These enzymes—aspartate aminotransferase [AST, or serum glutamate oxaloacetic transaminase (SGOT)] and alanine aminotransferase [ALT, or serum glutamate pyruvate transaminase (SGPT)] catalyze the transfer of the amino acids of aspartate and alanine to the keto group of ketoglutaric acid. ALT is primarily located in liver while AST is present in tissues like liver, skeletal muscle, kidney, heart, muscle, brain, pancreas, lung, leukocytes and red blood cells.

AST is present in both the mitochondria and cytosol of hepatocytes (isoenzymes), while ALT is a cytosolic enzyme with the highest concentrations in the liver. Elevation of the enzyme occurs due to destruction or change in cell membrane permeability of tissues rich in the aminotransferases allowing AST and/or ALT to leak from damaged cells into serum. Whether serum AST level elevation is of hepatic origin should be confirmed by obtaining a serum ALT level. About 80% of AST activity in human liver is contributed by the mitochondrial isoenzyme, whereas most of the circulating AST activity in normal people is derived from the cytosolic isoenzyme. Large increases in mitochondrial AST occur in serum after extensive tissue necrosis. Causes of deranged aminotransferases (AST and ALT) are listed in **Table 1**.

Aspartate aminotransferase:Alanine aminotransferase ratio (De Ritis ratio) This ratio may assist in differentiating the site of biliary obstruction. In a cholestatic picture, an AST:ALT ratio of less than 1.5 is suggestive of an obstruction outside liver. In such conditions the ALT titer is considerably higher than AST. An AST:ALT ratio of greater than 1.5 indicates intrahepatic (mechanical or medical)

Table 1 Causes of deranged aminotransferases (AST and ALT)

Mild elevation of AST and ALT (1–3 times)	Moderate elevation of AST and ALT (3–20 times)	Marked AST and ALT elevations (> 20 times, 1,000 U/L)	Isolated raised AST	Falsely low AST, ALT
<ul style="list-style-type: none"> Neonatal hepatitis EHBA Fatty liver Nonalcoholic steatohepatitis (NASH) Drug toxicity 	<ul style="list-style-type: none"> Wilson disease Autoimmune hepatitis Typhoid Malaria Celiac disease Medications Acute viral hepatitis Chronic hepatitis B and C 	<ul style="list-style-type: none"> Acute viral hepatitis Ischemic hepatitis Drugs Autoimmune hepatitis Acute Budd-Chiari syndrome 	<ul style="list-style-type: none"> Hemolysis Myopathy Thyroid disease Exercise Myocardial infarction 	<ul style="list-style-type: none"> Hemodialysis Pyridoxine deficiency Uremia

Abbreviations: AST, aspartate transaminase; ALT, alanine aminotransferase; EHBA, extrahepatic biliary atresia.

cholestasis. The ratio invariably rises to more than one as cirrhosis develops because of decreased plasma clearance of AST secondary to impaired function of sinusoidal cells and the lack of ALT rise is probably due to pyridoxine deficiency. Causes of abnormal AST:ALT ratio are listed in **Table 2**.

Wilson disease presenting as acute liver failure can be diagnosed with 100% sensitivity and specificity using the combination of an ALP:bilirubin ratio less than 4, along with an AST:ALT ratio of greater than 2.2. Also the AST:platelet ratio index (APRI) is an useful indicator but has poor sensitivity where an APRI greater than 1.5 signifies moderate to severe fibrosis.

Other enzymes that are deranged in hepatocellular necrosis are isocitrate dehydrogenase, glutamate dehydrogenase, lactate dehydrogenase and sorbitol dehydrogenase but none of these tests have proved to be useful in practice.

Enzymes that Detect Cholestasis

Alkaline phosphatase These are zinc metalloenzymes with a serine at center. These are present in nearly all tissues such as liver, kidney, bone, etc., with most circulating alkaline phosphatase originating from liver or bone in healthy people. It is found in the microvilli of bile canaliculi and on the sinusoidal surface of hepatocytes. Alkaline phosphatase from intestine and placenta are derived from different genes while that from liver, bone and kidney are thought to be from the same gene. Average values of alkaline phosphatase are relatively high in childhood, puberty and in old age while lower in middle age with males having higher values in comparison to females. Alkaline phosphatase reaches the circulation probably by leakage from the bile canaliculi into hepatic sinusoids. In drug-induced cholestasis there is preferential rise in ALP, rather than gamma-glutamyl transpeptidase (GGT) and an ALT:ALP ratio is less than 2. Causes of deranged alkaline phosphatase are listed in **Table 3**.

Glutamyl transpeptidase Gamma glutamyl transpeptidase is a membrane bound glycoprotein with gene on chromosome 22 which catalyzes the transfer of glutamyl group to other peptides, amino acids and water. The kidneys, pancreas, liver, intestine and prostate contain large amounts with men having higher values.

Table 2 Causes of abnormal AST:ALT ratio

AST:ALT > 2	AST:ALT < 1
<ul style="list-style-type: none"> Wilson disease Cirrhosis (CLD) Shock Alcoholic hepatitis 	<ul style="list-style-type: none"> Viral hepatitis Toxic hepatitis Autoimmune hepatitis Nonalcoholic steatohepatitis Cholestatic hepatitis

Abbreviations: AST, aspartate transaminase; ALT, alanine aminotransferase

Table 3 Causes of abnormal alkaline phosphatase

High alkaline phosphatase	Low alkaline phosphatase
<ul style="list-style-type: none"> Cholestatic disorders Acute viral hepatitis (normal or moderately increased) Infiltrative liver disease* Abscess Granulomatous liver disease Drugs: Antibiotics, immunosuppressants, tricyclic antidepressants and angiotensin converting enzyme inhibitors. Amyloidosis Bone metastasis* 	<ul style="list-style-type: none"> Wilson disease** Hypothyroidism Pernicious anemia Zinc deficiency Congenital hypophosphatasia

*Tumor specific isoenzymes are Regan, Nagao and Kasahara isoenzymes.

**Wilson disease complicated by hemolysis and fulminant hepatic failure (FHF) usually have low levels of alkaline phosphatase leading to low ratio of alkaline phosphatase and bilirubin in fulminant Wilson disease. Copper replaces cofactor zinc and might result in subsequent inactivation of alkaline phosphatase. This low ratio of alkaline phosphatase to bilirubin is associated with a poor prognosis.

Range varies from less than 385 U/L in less than 1 month, less than 225 U/L at 1–2 months and less than 135 U/L in 2–4 months age group with serum values similar to adults in children more than 4-year-old (0–30 IU/L). As it is not found in bone, so bone disease can be excluded if elevated GGT levels are found. Phenobarbitone and phenytoin lead to high GGT levels as they are enzyme inducers, on the contrary, valproic acid does not induce serum GGT levels, except in cases of true hepatotoxicity so this is good test for monitoring liver injury during valproate therapy. **Table 4** enlists important causes of deranged GGT.

5'-Nucleotidase 5'-Nucleotidase (5-NT) catalyzes the hydrolysis of adenosine-5-phosphate or inosine-5-phosphate. Though it is found in liver, intestines, brain, heart, blood vessels, and endocrine pancreas, its marked elevations are seen only with underlying liver disease. 5-NT is located in both sinusoidal and canalicular membranes in liver. Their levels are lower in children, increase gradually with adolescence and reach a plateau after 50 years of age. The abnormal 5-NT values usually mimic that of serum AP levels, as both enzymes have similar locations within the hepatocyte but 5-NT levels do not increase in the presence of bone disease, unlike alkaline phosphatase.

Leucine aminopeptidase These are zinc-dependent exopeptidases by which processing, catabolism and degradation of intracellular proteins occurs. This enzyme is normally found in cells of the liver and small intestine. Levels are raised in cholestasis, cirrhosis, hepatitis, ischemia (reduced blood flow to the liver), necrosis and tumor.

Table 4 Causes of abnormal GGT

High GGT	Low GGT
<ul style="list-style-type: none"> • Cholestasis • Paucity of bile ducts • PFIC3 • Sclerosing cholangitis • Acute viral hepatitis • Uncomplicated DM • Acute pancreatitis, MI • <i>Drugs:</i> Phenobarbitone, phenytoin, paracetamol, tricyclic antidepressants • Anorexia nervosa • Guillain-barré syndrome • Hyperthyroidism • Obesity, dystrophica myotonica 	<ul style="list-style-type: none"> • PFIC1, 2 • BRIC

Abbreviations: GGT, gamma-glutamyl transpeptidase; PFIC, progressive familial intrahepatic cholestasis; DM, diabetes mellitus; MI, myocardial infarction; BRIC, benign recurrent intrahepatic cholestasis.

TESTS OF THE BIOSYNTHETIC CAPACITY

Serum Proteins

Most of the serum proteins are synthesized in liver. Albumin, most of the α - and β -globulins, fibrinogen and other coagulation factors are produced in the parenchymal cells.

Albumin Albumin is a useful indicator of hepatic function. Its half life is around 20 days, so in acute liver disease, its level are not reliable indicator. The serum albumin levels tend to be normal in acute viral hepatitis, drug-induced hepatotoxicity and obstructive jaundice. Its levels are increased by corticosteroids and thyroid hormone while lower levels are seen in chronic liver disease (CLD) like cirrhosis. Normal serum values are 3.5–4.5 g/dL. Hypoalbuminemia is not specific for liver disease but may occur in chronic protein losing enteropathies, protein malnutrition and nephrotic syndrome.

Prealbumin The serum prealbumin level is 20–30 mg/dL. Its levels are reduced in liver disease probably due to decreased synthesis. Reduction in its level may precede alteration in serum albumin because of its short half life so its determination is useful in drug-induced hepatotoxicity where early fall may predict hepatotoxicity.

Serum ceruloplasmin It is an acute phase protein synthesized in the liver. Normal plasma levels are 20–40 mg/dL. The levels rise in infections, rheumatoid arthritis, non-Wilson liver disease, obstructive jaundice and in pregnant females. The plasma level is usually low in Wilson disease, neonates, protein losing enteropathy, copper deficiency, aceruloplasminemia, kwashiorkor, marasmus and Menkes disease.

Procollagen III peptide The serum concentration of this peptide increase with hepatic fibrosis, inflammation and necrosis. Serial measurement of procollagen III may be helpful in the follow-up of CLD.

Alpha-1 antitrypsin Alpha-1 antitrypsin, a glycoprotein, synthesized by liver is an acute phase protein and is an inhibitor of serine proteinases, especially elastase. Its normal concentration is 100–160 mg/dL. Its level increases with inflammatory disorders in children and in pregnancy and after oral contraceptive pills (OCP) in adults. The alleles are M, F, S, Z and null forms. Neonatal hepatitis is associated with PiZZ homozygotes. While in adults ZZ, MZ, SZ and FZ phenotypes are associated with cirrhosis. Its deficiency should be confirmed by quantitative measurement.

Alpha fetoprotein It is the principal protein in fetal plasma in early gestation and is subsequently present at very low levels. More

than 90% of patients with hepatocellular carcinoma (HCC) have raised levels except when HCC arises in noncirrhotic liver. Serial determination with rise in the values should raise the suspicion of HCC in cirrhotic patients. Raised values are also found in other liver diseases like in regeneration phase of acute hepatitis, chronic hepatitis, adenomas associated with tyrosinemia and in hepatic metastasis. Normal range is less than 10 mg/dL in children more than 6-month-old.

Prothrombin time (PT) Eleven blood coagulation factors like fibrinogen, prothrombin, labile factor, stable factor, Christmas factor, Stuart-prower factor, prekallikrein and high-molecular-weight kininogen are produced in liver. The extrinsic coagulation pathway is assessed by one stage PT which is expressed in seconds or as a ratio of the patient's PT to control PT. Normal control usually is 9–11s and a prolongation of more than 2s is considered abnormal. The prolonged PT is not specific for liver diseases and is seen in various deficiencies of coagulation factors, disseminated intravascular coagulation (DIC), and ingestion of certain drugs. If the PT returns to normal or improves by at least 30% within 24 hours of a single parenteral injection of vitamin K1 (5–10 mg), it indicates good liver parenchymal function while in parenchymal disease only minimal or no improvement is seen. Most patients with extrahepatic obstruction like extrahepatic biliary atresia (EHBA) would respond promptly to a single injection of vitamin K1 unlike some inherited metabolic diseases in the newborn, such as tyrosinemia in which the profound prolongations of both PT and partial thromboplastin time (PTT) may appear out of proportion to other parameters of liver dysfunction. It is important to perform PT/partial thromboplastin time activated with kaolin (PTTK) before invasive procedures like liver biopsy and kidney biopsy. The PT test is not a sensitive index of CLD but has high prognostic value for patients with acute hepatocellular disease. A persistently abnormal PT in a previously well child can be the single laboratory test that can predict the possibility of the development of acute liver failure. Many of the clotting factors, including the vitamin K-dependent factors II, VII, IX, and X, are less than 70% of adult levels in both full-term and preterm newborns. The hemostatic system of the neonate is dynamic and evolves toward that of normal adult. Normal values at various ages in postnatal period need to be considered. Normal values of PT and activated PTT are given in **Table 5**.

Fibrinogen Low levels of fibrinogen are seen in liver disease accompanied by DIC when there is consumption of fibrinogen and other clotting factors. Conversely, high levels may be seen in patients with hepatic diseases because fibrinogen is an acute phase reactant or because of elevations described specifically in cholestatic disease. Some patients with liver disease develop a dysfibrinogenemia with an abnormal fibrin monomer aggregate, which is manifested by a normal measured fibrinogen level.

Lipids and Lipoproteins

The liver plays a central role in production and degradation of lipoproteins. The cholesterol is transported in the blood in lipoprotein X, a lipoprotein specific to cholestasis. However, in noncholestatic liver diseases, declining lipoprotein cholesterol

Table 5 Reference values for prothrombin time (PT) and activated partial thromboplastin time (aPTT) in infants

Postnatal age	PT, Seconds	Activated PTT, Seconds
1 month	11.8 (10.0–13.6)	44.7 (26.9–62.5)
3 months	12.3 (10.0–14.6)	39.5 (28.3–50.7)
6 months	12.5 (10.0–15.0)	37.5 (21.7–53.3)

Source: Andrew M, Paes B, Milner R, et al. Development of the coagulation system in the healthy preterm infant. *Blood*. 1988;72:165–7.

may reflect deteriorating liver function and may be an indicator of prognosis. In acute hepatocellular injury there is mild hypertriglyceridemia secondary to decrease in levels of hepatic enzymes such as lecithin-cholesterol acyltransferase (LCAT) and triglyceride lipase (TGL).

Bile Acid Tests

Bile acids are a class of endogenous organic anions synthesized from cholesterol exclusively in the hepatocytes, conjugated to glycine or taurine and then secreted into bile. Measuring serum bile acids may not be as useful a test in children because of the presence of a relative physiologic cholestasis in neonates, which results in baseline elevations of serum levels even in healthy babies. These baseline elevations decrease within the 1st year of life, indicating a maturation of the bile acid transport processes. Serum bile acids are disproportionately elevated in primary sclerosing cholangitis and progressive familial intrahepatic cholestasis (PFIC) syndromes (subtypes 1, 2 and 3) even when the serum bilirubin is normal. The development of the technique of fast atom bombardment mass spectrometry has allowed the rapid screening of urine samples from infants and older children with suspected bile acid synthetic disorders using microliter amounts of sample directly.

TESTS BASED ON SUBSTANCES CLEARED FROM PLASMA BY THE LIVER

Ammonia

The concentration of ammonia in the blood is regulated by the balance of its production and clearance. Production is mainly in the large intestine by the action of bacterial urease on dietary protein and amino acids. Clearance of ammonia occurs mainly in the liver via transformation of ammonia into urea via the urea cycle and into glutamine by transamination of α -ketoglutarate to glutamate and then to glutamine. The liver ordinarily removes 80% of the portal venous ammonia in a single pass. In CLDs, disturbed urea cycle function caused by parenchymal liver cell destruction and portosystemic shunts permit large amounts of ammonia to bypass the liver and exert their effects on the central nervous system. Some ammonia is also made by the kidney and small intestine, a fact that becomes important when a patient is taking certain drugs like valproic acid, which can cause an increase in serum ammonia independent of any hepatotoxicity because of the drug-induced ammonia production by the kidney.

Exogenous Substances Used in Tests to Assess Quantitative Liver Function

The tests for quantitative liver function or true dynamic liver function are based on uptake, metabolism and excretion of a determinate substance. The ideal test would be inexpensive, easy to perform and analyze, safe, have a single pharmacokinetic profile with minimal drug interactions, high predictive value and with quick results. Dynamic function tests can be either those using elimination of a substrate for testing (e.g., indocyanine green clearance, caffeine clearance and galactose elimination) or those that detect metabolites of the substance administered [e.g., aminopyrine breath test, monoethylglycinexylidide (MEGX) test, and para-aminobenzoic acid (PABA) test]. MEGX testing is important in evaluating liver function to determine the suitability of the donor liver for transplant and to measure graft function post transplantation. PABA is a nontoxic, inexpensive and orally administered probe drug that is readily absorbed from the gastrointestinal tract and undergoes biotransformation to three metabolites independent of phase I cytochrome P450 biotransformation reactions which are lost in patients with

extensive hepatocellular damage. Through phase II conjugation reactions, PABA combines with either glycine [to form para-aminohippuric acid (PAHA)]; acetyl-coenzyme A (CoA) [to form para-acetamidobenzoic acid (PAABA)]; or both glycine and acetyl CoA [to form para-acetamidohippuric acid (PAAHA)]. The use of PABA to quantify hepatic function has been reported to be a promising prognostic test for children with both CLD and fulminant liver failure with a sensitivity of 92% and negative predictive value of 92% compared with a sensitivity of 54% and a negative predictive value of 63% with King's College criteria.

OTHER LABORATORY TESTS TO ASSESS FOR LIVER DISEASE

Serum Globulins

The serum globulin level can be quickly determined by subtracting the albumin concentration from the total protein level. Serum globulins can be further separated by using serum protein electrophoresis into α_1 , α_2 , β , and γ fractions. The α_1 fraction is composed principally of α_1 -antitrypsin, ceruloplasmin and orosomucoid, all of which are acute-phase reactants and increase in response to liver disease and many inflammatory disorders. Haptoglobin makes up a large part of the α_2 fraction. Transferrin and β -lipoprotein make up a major portion of the β fraction. The principal constituents of the γ fraction are the immunoglobulins (Ig), particularly IgG, IgA and IgM. Abnormalities may occur in the serum protein electrophoresis profile in various liver diseases, such as hypergammaglobulinemia seen in autoimmune hepatitis and low α_1 peak in α_1 -antitrypsin deficiency.

Plasma and Urine Amino Acids

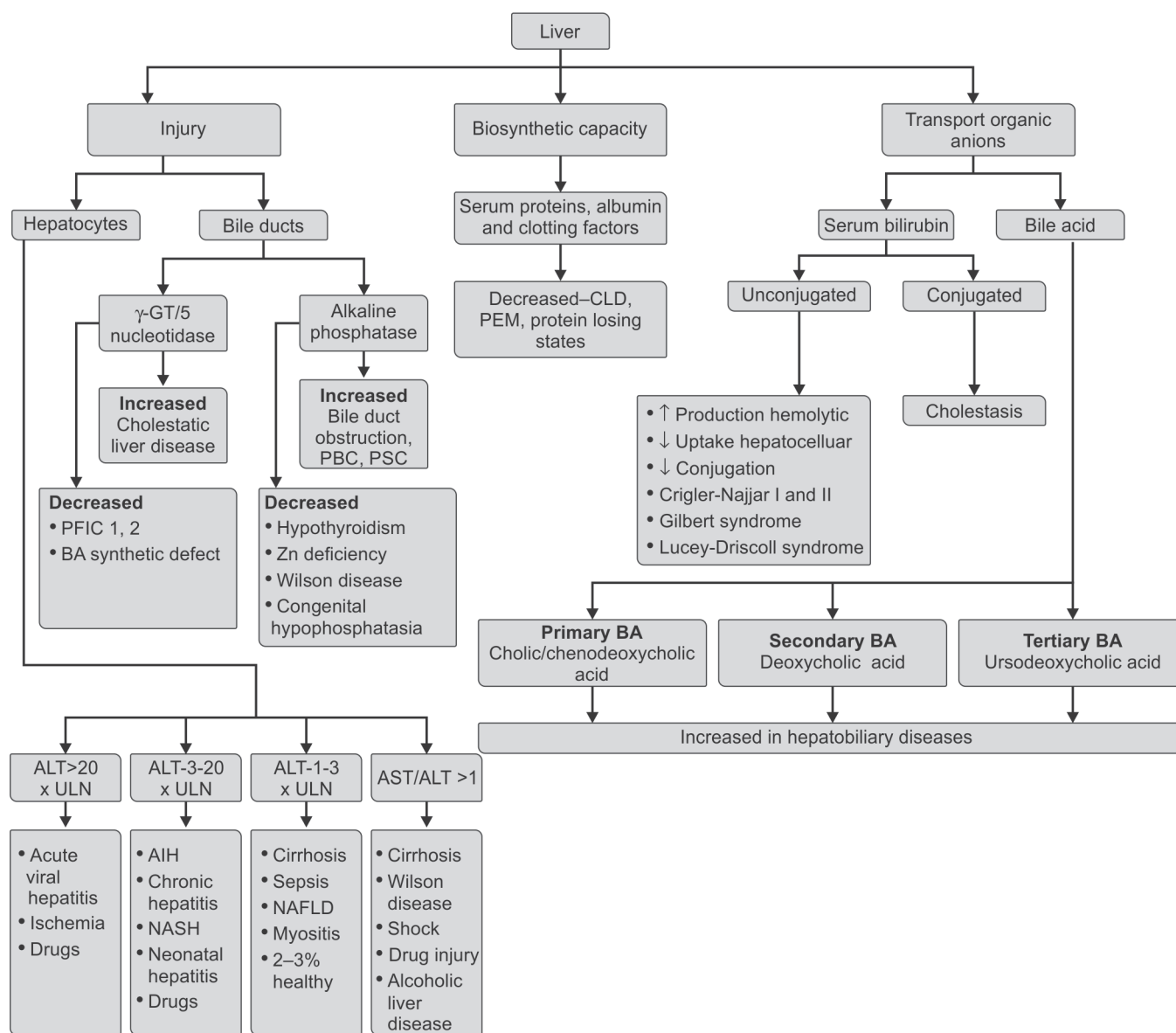
Amino acids in the blood and urine may help to support the diagnosis of an inborn error of intermediary metabolism, such as hereditary tyrosinemia, methylmalonic acidemia and defects of urea cycle defects.

An approach to liver functions tests is summarized in **Flow chart 2**.

IN A NUTSHELL

1. Liver enzymes are commonly used in the evaluation of patients with a range of liver diseases, but they lack sensitivity and the specificity.
2. Alanine transaminase is a very specific marker of hepatocellular injury with relatively low concentration in other tissues.
3. Aspartate transaminase occurs in two isoenzymes which are the mitochondrial isoenzyme more specific to liver and cytosolic isoenzyme which is present in skeletal muscle, heart muscle and kidney tissue.
4. Aspartate transaminase usually rises in conjunction with ALT to indicate a hepatitis picture. An AST:ALT ratio of less than 1 is seen in viral hepatitis, autoimmune hepatitis, nonalcoholic steatohepatitis (NASH), toxic and cholestatic hepatitis while AST:ALT ratio of greater than 2 suggests cirrhosis, ischemia, Wilson disease, or alcoholic liver disease.
5. Elevation of GGT with high ALP is suggestive of biliary tract obstruction.
6. Synthetic function of liver is assessed by albumin and PT.
7. Low alkaline phosphatase is commonly seen in Wilson's disease, hypothyroidism and zinc deficiency.
8. Prothrombin time has a better prognostic value for patients with acute hepatocellular disease.
9. In a setting of underlying liver disease, worsening of PT is suggestive of decompensation of liver.

Flow chart 2 Approach to liver function tests



Abbreviations: AST, aspartate transaminase; ALT, alanine aminotransferase; PSC, primary sclerosing cholangitis; PBC, primary biliary cirrhosis; CLD, cholestatic liver disease; PEM, protein-energy malnutrition; NASH, nonalcoholic steatohepatitis; PFIC, progressive familial intrahepatic cholestasis; NAFLD, nonalcoholic fatty liver disease; ULN, upper limit of normal.

MORE ON THIS TOPIC

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Chapter 37.3

Neonatal Cholestasis

Surender Kumar Yachha, Moinak Sen Sarma

Neonatal cholestasis is defined as impaired canalicular biliary flow in a neonate resulting in accumulation of bilirubin, bile acids and cholesterol in blood and extrahepatic tissues. Though some of the disorders may be clinically evident after the first month of life, anytime later in the infancy, these diseases are still classified as neonatal cholestasis as the etiology is believed to be since birth. Conjugated hyperbilirubinemia is defined as direct bilirubin level greater than 1 mg/dL when total bilirubin is less than 5 mg/dL or greater than 20% of total bilirubin if greater than 5 mg/dL.

Table 1 elaborates the common causes of neonatal cholestasis in India. Out of all the causes, the thrust is early diagnosis and management of potentially treatable conditions by pediatricians. Biliary atresia has a time bound progression and needs early intervention. Metabolic disorders like galactosemia, neonatal hemochromatosis and tyrosinemia are sick neonates who deteriorate rapidly.

Reasons for Delay in Referral

- Misdiagnosed as physiological jaundice or breastmilk jaundice
- Babies may look well, feed well, develop normal social smile giving a false impression of well-being to parents
- Lack of awareness at primary and secondary levels of care to prioritize referral
- Lack of clarity in clinical approach to promptly diagnose the underlying cause.

Hence, it is imperative for every pediatrician to ask for diaper staining of urine and look for organomegaly in any neonate with jaundice suggesting conjugated jaundice. Any infant beyond 2 weeks of life with cholestasis should be immediately evaluated. However, there are disorders that may present in first 2 weeks of life particularly metabolic diseases and infection like herpes simplex virus (HSV).

Stool Color in Neonatal Cholestasis

Pale stools can be present in extrahepatic or intrahepatic causes as shown in **Figure 1**. Pigmented stools point toward an intrahepatic etiology. However, the color may often be ambiguous causing confusion in interpretation. It is important for the pediatrician to see for himself 3–4 consecutive stools samples in a transparent container against a well-lit contrast background to decide on the color. Pale stool documentation indicates a very high possibility of nonflow of bile into small intestine thus warranting an early referral and urgency to diagnose biliary atresia.

Coagulopathy in Neonatal Cholestasis

During the course of the disease, child may have overt coagulopathy features such as spontaneous skin bleeds, muscle hematoma during immunizations or intracranial bleed. Coagulopathy is correctable with vitamin K particularly in extrahepatic causes.

Who is a Sick Neonate?

Other than lethargy, poor feeding, and seizures in a cholestatic neonate there are features that must always alarm the pediatrician



Figure 1 Pale stools in neonatal cholestasis

Table 1 Etiology of 1,008 cases of neonatal cholestasis (combined data of 8 medical centers in India)

Disease groups	Causes in each subgroup
A. Hepatocellular 53% (n = 533)	
Neonatal hepatitis 47% (n = 468)	<ul style="list-style-type: none"> • Idiopathic giant cell hepatitis 64%. • TORCH infections 22% (CMV, 58%; toxoplasmosis, 23%; hepatitis, 10%; rubella, 4.5%; syphilis, 4%; and herpes 1%). • Sepsis, 8%. • Other causes like malaria, UTI, etc., 6%.
Metabolic 4% (n = 43)	Galactosemia, 35%; AIAT deficiency, 33% (suspected);* TPN related, 19%; tyrosinemia, 7%; storage disorders, 4%; hemochromatosis, 2%.
Other causes 2% (n = 22)	Inspissated bile plug syndrome (n = 9), recurrent intrahepatic cholestasis (n = 2), progressive familial intrahepatic cholestasis (n = 1), hypothyroidism (n = 4), associated Down's syndrome (n = 3); and one case each of polycystic disease, postintestinal surgery and immunodeficiency.
B. Obstructive 38% (n = 383)	Biliary atresia, 34%; Choledochal cyst, 4%.
C. Ductal Paucity 3% (n = 29)	Syndromic variety, 17%; nonsyndromic variety, [†] 83%.
D. Unknown 6% (n = 63)	

*Recent studies using confirmatory test of isoelectric focusing reported 57/58 children of liver disease having normal PiMM phenotype.

[†]Mostly now considered secondary to other causes and not as a primary defect.

warranting early workup. These are uncorrectable coagulopathy, hypoglycemia, ascites, family history of early infantile sib deaths, maternal history of stillbirths, abortions, associated fever, anemia or respiratory distress.

Tables 2 and 3 enlist the common causes of neonatal cholestasis with their presentation and the clinical evaluation of intrahepatic causes of neonatal cholestasis.

BILIARY ATRESIA

Biliary atresia is an idiopathic inflammatory process involving the bile ducts resulting in obstruction of biliary tract, chronic cholestasis and progressive fibrosis that eventually causes biliary

cirrhosis and end-stage liver disease. Etiopathogenesis is unclear. Viruses, autoimmunity and genetic susceptibility have been proposed, but there is no convincing disease-causal relationship. There are no racial or familial predispositions. Incidence is 1:15,000 in Asia. Biliary atresia may exist in isolation (90%) or as a part of a larger syndrome (10%). Biliary atresia may be associated with polysplenia, situs inversus, malrotation of gut and cardiac anomalies (biliary atresia splenic malformation). This condition has a worse outcome in view of the comorbidities. **Figures 2A to F** elaborates the three anatomical types of biliary atresia. Cystic dilatations may be seen in 6–22% of cases (**Figs 3 and 4**), mostly extrahepatic and should not be confused with choledochal cyst on imaging. Biliary atresia presents as normal birthweight, apparently healthy baby with persistently pale stools. As age advances in an unoperated child, features of decompensation appear in the form of deepening of jaundice and presence of ascites (**Fig. 5**).

Management

Liver functions in biliary atresia are not discriminatory with regard to other intrahepatic causes except that it might show high gamma-glutamyl transpeptidase. Ultrasonography, liver biopsy and hepatobiliary scintigraphy features are shown in **Table 4** and **Figures 6 to 8**. Due to procedural technical difficulties and poor diagnostic accuracy, endoscopic retrograde cholangiopancreatography and magnetic resonance cholangiopancreatography are not popular in the work-up algorithm. In developing countries, liver biopsy should be done to decrease the frequency of negative laparotomy and to achieve cost-benefit with reduced morbidity. Laparotomy and per-operative cholangiography (gold standard) is performed wherever possible to have final confirmation of biliary atresia (**Figs 9 and 10**).

The most common form of biliary atresia is type III which requires Kasai portoenterostomy (**Fig. 11**). Hepaticojejunostomy is done for types I and II. Success of the surgery is based on the anatomical findings, age at surgery and the experience of the surgeon. Best option is to perform surgery between day 28 and day 60 of life. Outcome progressively decreases as the age

Table 2 Common causes of neonatal cholestasis and their presentation

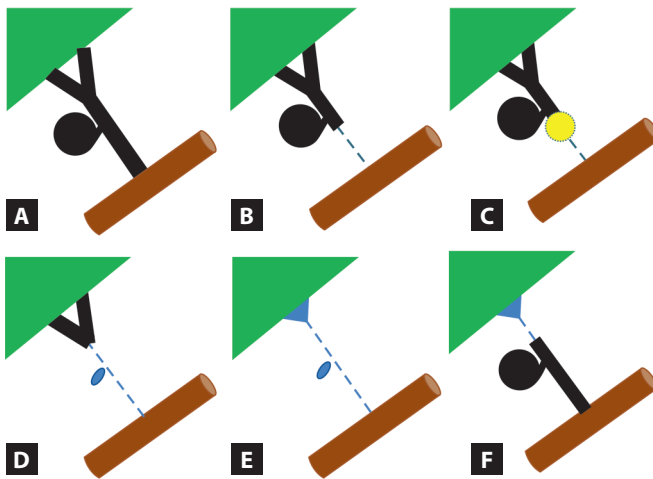
	Extrahepatic	Intrahepatic
Nonsick	Biliary atresia Choledochal cyst (CC)	Progressive familial intrahepatic cholestasis (PFIC) Paucity of interlobular bile ducts (PILBD) (syndromic or nonsyndromic) Idiopathic neonatal hepatitis Niemann–Pick disease (type C)
Sick	Biliary atresia with superimposed infections, CC with cholangitis	Galactosemia Tyrosinemia Neonatal hemochromatosis (NH) Mitochondrial hepatopathies* (MH) Herpes simplex virus infection (HSV) Hemophagocytic lymphohistiocytosis (HLH) Niemann–Pick disease (type C): rarely

*Mitochondrial hepatopathies include respiratory chain and fatty acid oxidation defects.

Table 3 Clinical evaluation of intrahepatic causes of neonatal cholestasis

Onset of jaundice	<ul style="list-style-type: none"> At birth: NH, HSV Few weeks after birth: PFIC type II, galactosemia Delayed-onset (after 1 month): Tyrosinemia, PFIC type I Any point of time: MH, HLH
Affected sib or sib death	Galactosemia, tyrosinemia, MH, HLH, PFIC, Alagille
Seizures	<ul style="list-style-type: none"> Hypoglycemia: Galactosemia Intracranial bleed: All conditions CNS infection: HSV
Maternal clues	<ul style="list-style-type: none"> Genital vesicles: HSV Oligoamnios, megaplacenta: NH Antenatal pruritus (3rd trimester) with similar history in maternal sisters or grandmother: PFIC Pruritus on oral contraceptives: PFIC Acute fatty liver of pregnancy: FAOD (long chain disease) Hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome: FAOD (long chain disease)
Early-onset ascites	Galactosemia, tyrosinemia, NH, MH, HLH
Shrunk liver	NH (not in all but in a subset)
Splenohepatomegaly	HLH, Niemann–Pick disease type C
Peripheral findings	<ul style="list-style-type: none"> Scalp vesicles: HSV Cataract: galactosemia Cabbage odor urine: tyrosinemia Rickets (craniotabes): tyrosinemia Hypotonia: MH, Niemann–Pick disease type C

Abbreviations: PFIC, progressive familial intrahepatic cholestasis; NH, neonatal hepatitis; HSV, herpes simplex virus; MH, mitochondrial hepatopathies; HLH, hemophagocytic lymphohistiocytosis; FAOD, fatty acid oxidation defects.



Figures 2A to F Anatomical types of biliary atresia: (A) Normal biliary tract; (B) Type I (5%): common bile duct (CBD) obliterated with patent proximal system. Good sized noncontractile gallbladder; (C) Type I with cyst. A cyst may appear anywhere in the biliary system just proximal to site of obstruction (seen with all three types); (D) Type II (3%): Obliterated CBD and common hepatic duct (CHD) but patent right and left hepatic ducts. Absent or rudimentary gallbladder; (E) Type III (>90%): Entire biliary tract obliterated with fibrous mass at porta. Absent or rudimentary gallbladder; (F) A variant of type III where ducts at porta are obliterated but distal CBD is patent. Good sized non-contractile gallbladder

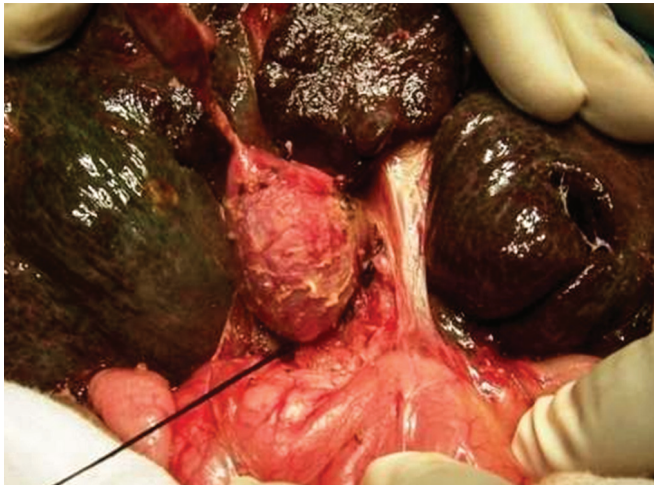


Figure 4 Biliary atresia with cyst seen at surgery

advances. The success of surgery is shown by the excretion of bile and improvement of jaundice. Ascending cholangitis occurs in 30–60% of cases following Kasai surgery, mostly due to gram-negative rods. Portal hypertension develops if the disease takes a progressive course. Approximately 75% develop variceal bleeds by the age of 2 years. After surgery, the survival rate with native liver is 32–60% after 5 years and between 22% and 53% after 10 years. On long-term follow-up, children with successful portoenterostomy by adolescence require liver transplantation in 85% cases and 15% have symptom-free survival with native liver. Despite this outcome, portoenterostomy remains the first-line treatment of biliary atresia as it allows children to escape immunosuppressive drug treatment due to liver transplantation for a long period of time and a proportion can still survive without transplantation.

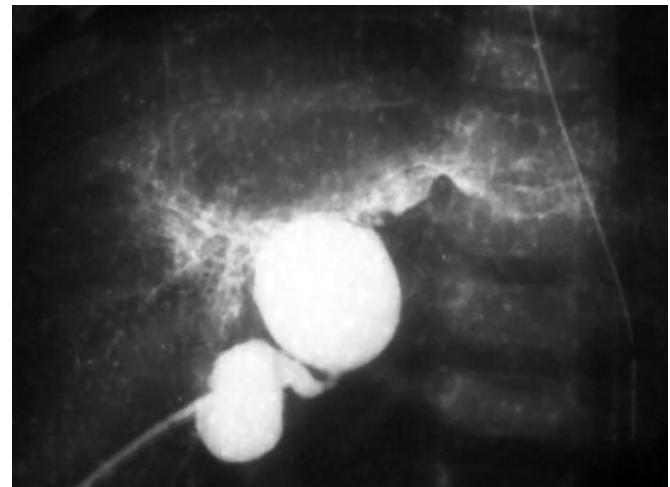


Figure 3 Biliary atresia with cyst. Paucity of contrast in intrahepatic ducts seen in peroperative cholangiogram



Figure 5 Decompensated biliary atresia at advanced age

GALACTOSEMIA

It is an autosomal recessive disorder of galactose metabolism, caused by a deficiency of the enzyme galactose-1-phosphate uridylyltransferase (GAL-1-PUT). In the absence of this enzyme, galactose is converted to a toxic byproduct, galactitol, that affects the liver, brain, kidneys, and eyes by its osmotic property. Lactose, a disaccharide is broken down to glucose and galactose by brush border enzymes in the small bowel. Therefore, lactose is a rich source of exogenous galactose. Clinical manifestations may appear soon after ingestion of galactose (breastmilk/formula feeds). These include jaundice, hepatosplenomegaly, liver dysfunction, coagulopathy, hypoglycemic seizures, renal tubular dysfunction, cataract (bilateral), *Escherichia coli* sepsis (common), and rarely

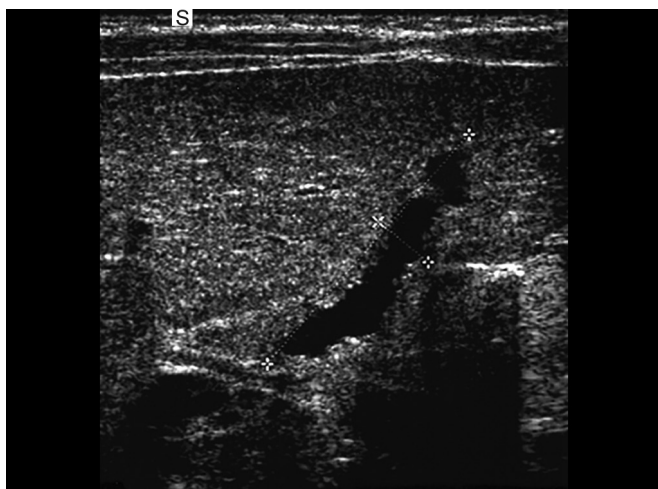


Figure 6 Atretic gallbladder (irregular margins and contour) on USG in biliary atresia

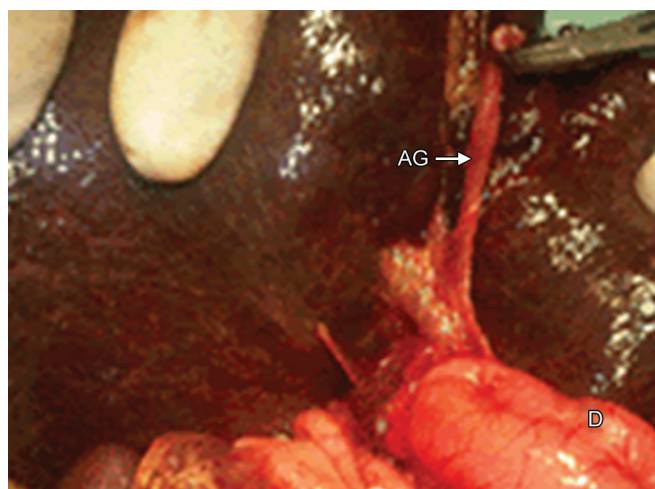


Figure 7 Atretic gallbladder seen at surgery

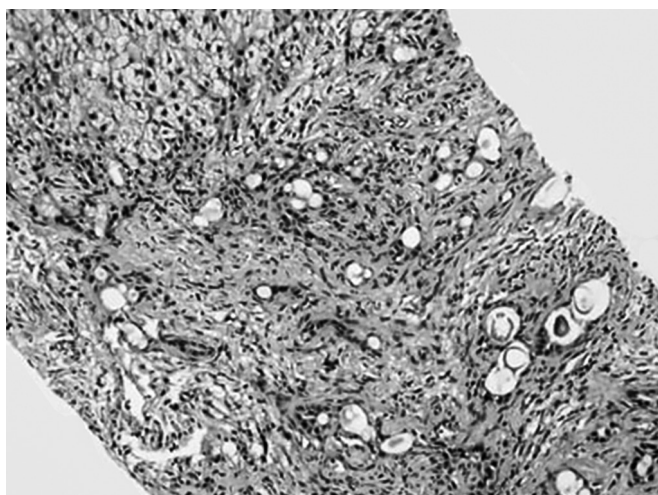


Figure 8 Histopathology in biliary atresia (BA) showing bile ductular proliferation and portal fibrosis

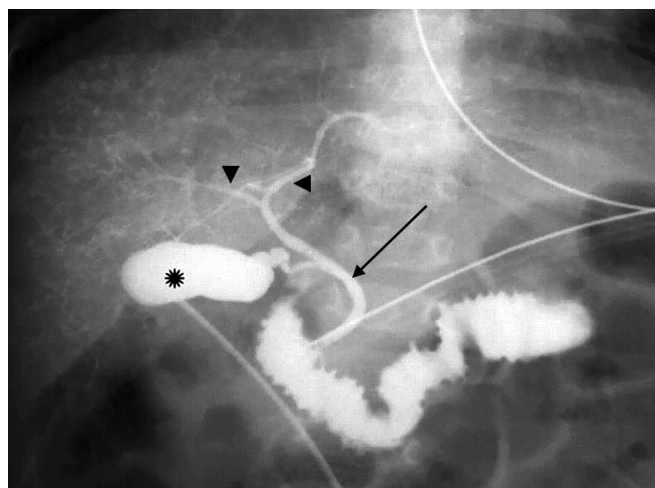


Figure 9 Normal peroperative cholangiogram



Figure 10 Type III biliary atresia (BA) cholangiogram. No contrast in biliary tree

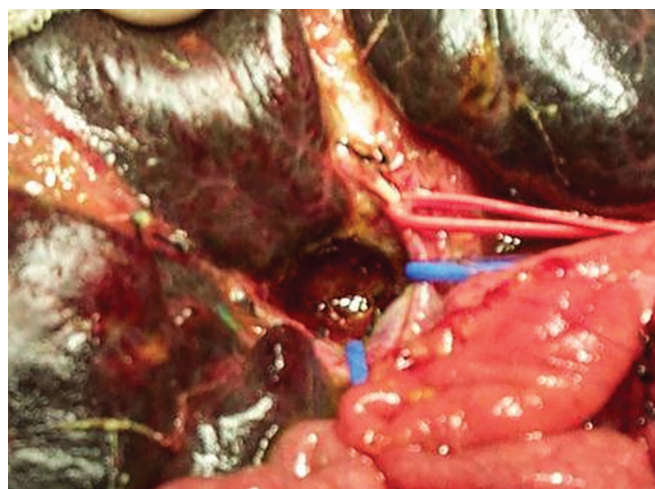


Figure 11 Kasai portoenterostomy: wide dissection at portal plate followed by attachment of roux-en-Y isoperistaltic jejunal loop at porta

hemolysis. If untreated, rapid downhill course may result in progressive liver disease, cirrhosis, and death. Activity of enzyme GAL-1-PUT activity in red blood cells is low or absent. Therapy

is supportive. Lactose-free diet is the mainstay of treatment. Stop breastmilk, animal or formula feeds in the neonate, and change over to nonlactose formula feeds. Soy-based feeds, though not

recommended in neonates are the only option presently in India as lactose-free formulations are not available (compulsion). Restriction of milk or milk products is lifelong. Restriction of galactose-containing fruit and vegetables is not currently recommended. Long-term liver outcome is good on galactose restricted diet. However, a subset (25–50%) in the long run have speech apraxia, language impairment and lower intelligence quotient due to endogenous production of galactose.

PROGRESSIVE FAMILIAL INTRAHEPATIC CHOLESTASIS

Progressive familial intrahepatic cholestasis (PFIC) is a group of genetic disorders that show progressive intrahepatic cholestasis with autosomal recessive inheritance. PFIC1 (original Byler disease) is caused by mutations of the *FIC1* gene located on chromosome 18q21-22, which encodes a P-type ATPase protein involved in aminophospholipid transport. The defect is in the intestine as well. PFIC2 is due to mutations of the *SPGP* (sister of P-glycoprotein) gene encoding the ATP-dependent canalicular bile acid transporter (also called BSEP, bile salt export pump) located on chromosome 2q24. PFIC3 is due to mutations of the *MDR3* (multidrug resistance 3) gene encoding the biliary phospholipid transporter and is located on chromosome 7q21. Clinical features, investigations and treatment of each subtype are listed in **Table 4**.

ALAGILLE SYNDROME

This autosomal dominant disorder is a syndrome of *paucity of interlobular bile ducts*. Mutations in human *JAG-1* gene (on chromosome 20p) or *Notch-2* gene are responsible. Diagnostic criteria are listed in **Box 1**. Associated anomalies include those of kidneys (small kidneys, ureteropelvic obstruction, renal tubular acidosis), or arteries (aneurysms or stenoses of intracranial, internal carotid or renal arteries).

Problems can occur in childhood and later in life. These include intractable pruritus due to cholestasis, disfiguring xanthomas (**Fig. 14**) due to hyperlipidemia, bony fractures due to vitamin D deficiency, and poor quality of life particularly due to pruritus. Almost 20% progress to cirrhosis. Major cause of mortality is related to cardiac disease and vascular events.

Treatment consists of (1) management of pruritus, (2) supplementation of multivitamins, vitamin D and calcium, and (3) biliary diversion in those with refractory pruritus and disfiguring xanthomas. Liver transplant is required for those with poor quality of life, progressive liver disease, and cirrhosis.

BOX 1 Criteria for diagnosis of Alagille syndrome

Paucity of interlobular bile ducts (PILBD) on liver biopsy + any three of five features below:

1. Chronic cholestasis (80% begin in neonatal period)
2. Characteristic facies (broad forehead, small chins and saddle nose with bulbous tip and hypertelorism (**Fig. 12**))
3. Skeletal abnormalities: Butterfly vertebrae T6-T9 (**Fig. 13**), curved phalanges and short ulna
4. Cardiac anomalies (peripheral pulmonary artery stenoses, tetralogy of Fallot)
5. Ocular anomalies:
 - Posterior embryotoxon (prominent white ring of Schwalbe at corneo-ueveal junction) on slit-lamp examination,
 - Optic nerve drusen (globules of calcified mucoproteins) on funduscopy

Note:

In the absence of liver biopsy finding, any four of five criteria.

No clinical criteria is required if suspicion is high and *JAG-1* or *NOTCH-2* mutation is detected.

NEONATAL HEMOCHROMATOSIS

This is an alloimmune gestational disease causing abnormal iron handling in utero by neonate and/or mother. The disorder presents as neonatal liver failure, ascites and hypoalbuminemia. A subgroup has shrunken nodular liver at birth as cirrhosis begins



Figure 12 Characteristic facies in Alagille syndrome

Table 4 Investigations for biliary atresia

Investigations	Findings	Comments
Ultrasound	One of the following <ul style="list-style-type: none"> • Absent GB • Rudimentary GB (length <15 mm with irregular mucosal lining and contour) • Good sized, noncontractile GB (size > 20 mm but prefeed-postfeed contractility < 50%) ± • Triangular cord sign (echogenic area > 4 mm in size anterior to right branch of portal vein)	Diagnostic accuracy 75–95%
Liver biopsy	• Bile ductular proliferation, fibrosis and widening of portal tracts (not before 4 weeks of age)	Diagnostic accuracy 88–97%
Scintigraphy	<ul style="list-style-type: none"> • Priming: ursodeoxycholic acid (30 mg/kg/day in 2–3 divided doses) for three days • Radioactivity in duodenum indicates patent biliary system that rules out biliary atresia • No excretion does not confirm biliary atresia • To be performed when stools are ambiguous in color • Not useful when stools are pale 	Adjunct in diagnosis



Figure 13 Butterfly vertebra



Figure 14 Xanthelasma in Alagille syndrome

in utero. Another presentation could be extrahepatic siderosis (pancreas, salivary glands, myocardium, thyroid), with sparing of reticuloendothelial system. There is history of recurrent sib deaths, oligoamnios and megaplacenta.

Investigations reveal (1) low or normal transaminases; (2) high serum ferritin: median 2,448 (range: 415–100,000) $\mu\text{g/L}$, low serum transferrin, and high transferrin saturation; confirmation is by lip biopsy: salivary gland biopsy shows iron deposition on staining (best for Indian situations) or MRI pancreas with low signal intensity on T2 imaging confirms the diagnosis.

Treatment

- Antenatal intravenous immunoglobulin (IVIG) infusion (1 g/kg) weekly to the mother from 18th week to term for at-risk pregnancies (70% neonates survive without transplant). This is offered where there is history of earlier sib death due to neonatal hemochromatosis.
- IVIG \pm exchange transfusion for symptomatic neonates (survival 75%).
- Liver transplantation is the only definitive treatment if medical treatment fails. Chelation and antioxidants are no longer used.

TYROSINEMIA TYPE 1

This is an autosomal recessive disorder causal due to deficiency of fumarylacetoacetate hydrolase in tyrosine metabolism. The

child may present with one or more of the following features: neonatal liver failure; acute liver failure in first 2 years of life (the most common presentation); chronic liver disease in childhood (ascites, coagulopathy); boiled cabbage odor of urine; renal tubular dysfunction; hypophosphatemic rickets; neurologic crises (peripheral neuropathy); and hepatocellular carcinoma (HCC) by 1st or 2nd decade.

Investigations reveal mildly raised bilirubin and transaminases. Serum alpha-fetoprotein is high (average: 160,000 $\mu\text{g/mL}$; normal full-term neonates: 84,000 $\mu\text{g/mL}$). Mass spectrometry reveals increased succinylacetone in urine and blood.

Treatment

- Dietary restriction of phenylalanine and tyrosine (formulation not marketed in India).
- Nitisinone is a potent inhibitor of 4-hydroxyphenylpyruvate dioxygenase and has been shown to efficiently prevent tyrosine degradation, and production of succinylacetone. Survival without liver transplant is 85% if started early at dose of 1–2 mg/kg/day (not marketed in India).
- Liver transplantation in failed nitisinone therapy, end-stage liver disease.

TORCH INFECTIONS

Contrary to the popular belief that TORCH is a major cause of neonatal cholestasis. It is now clear that positive TORCH titers are a *red herring* in the workup of a neonate with cholestasis. Except for acquired HSV infection which has rapid deterioration, the rest of the TORCH infections rarely cause jaundice. Acquired cytomegalovirus (CMV) is very rare and affects 1–2.5% newborns in first 90 days of life. Neonatal hepatitis is self-resolving and requires only supportive therapy. Suspicion of CMV hepatitis is raised when there are other stigmata: microcephaly, cataract, chorioretinitis or periventricular calcification. Serum IgM CMV positivity does not mean active liver replication. It is mandatory to demonstrate CMV DNA by the polymerase chain reaction (PCR) or culture in liver tissue \pm histological changes (inclusion bodies in vascular endothelium). CMV associated with biliary atresia is a highly doubtful entity, and it often delays referral. It should not be treated or pursued.

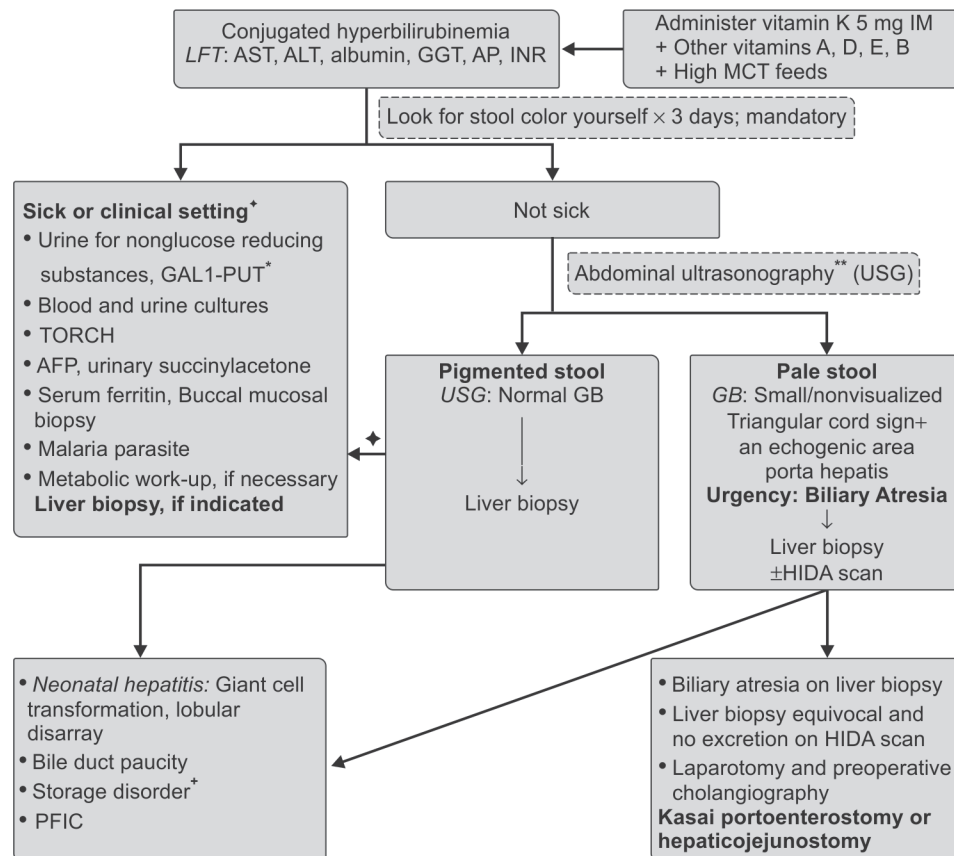
Herpes simplex virus infection is acquired in utero, perinatal period (85%), or postnatal period. No history is available in 60–80% of mothers. The child may present with poor feeding, lethargy, vesicles, seizures, renal failure, and ascites. Mortality is high if not treated on time. Suspect HSV infection in a sick neonate presenting in first week of life especially if bacterial cultures are sterile. Positive HSV cultures from vesicles, oropharynx, conjunctiva, blood, or cerebrospinal fluid (CSF) are diagnostic. Treatment consists of high dose acyclovir 60 mg/kg/day for 21 days, but is often continued till PCR for HSV is negative. It is essential to document negative CSF PCR at the end of therapy.

IDIOPATHIC NEONATAL HEPATITIS

It is a diagnosis of exclusion, usually seen in low birthweight or preterm babies. The infants are otherwise well and thriving. Stools are pigmented or pale. Resolution is spontaneous. Organomegaly disappears in 4–6 months. Liver function test normalizes in 4–12 months (average: 9 months). Liver biopsy reveals lobular disarray, hepatocyte ballooning, giant cell transformation, and extramedullary hematopoiesis. Therapy is supportive. Follow-up is necessary to document and finally label as idiopathic neonatal hepatitis, when the liver dysfunction has normalized.

MANAGEMENT OF NEONATAL CHOLESTASIS

Refer to **Flow chart 1** and **Tables 5** and **6**.

Flow chart 1 Approach to a case of neonatal cholestasis

Abbreviations: GB, gallbladder; MCT, medium chain triglycerides; AST, aspartate aminotransferase; ALT, alanine aminotransferase; AP, alkaline phosphatase; GGT, gamma-glutamyl transpeptidase; INR, international normalized ratio.

*Individualize investigations; *Stop milk feeds till galactosemia is ruled out; **Surgery, if choledochal cyst on USG, small gallbladder may also occur in bile duct paucity; *May need bone marrow testing.

IN A NUTSHELL

1. Neonatal cholestasis is defined as impaired canalicular biliary flow in a neonate resulting in accumulation of bilirubin, bile acids and cholesterol in blood, and extrahepatic tissues.
2. Common causes of neonatal cholestasis in India are hepatocellular causes (53%), and obstructive reasons (38%). Neonatal hepatitis and biliary atresia are the most frequent causes of hepatocellular and obstructive cholestasis, respectively.
3. Biliary atresia presents as normal birthweight, apparently healthy baby with persistently pale stools. As age advances in an unoperated child, features of decompensation appear in the form of deepening of jaundice and presence of ascites.
4. The most common form of biliary atresia is type III which requires Kasai portoenterostomy. Hepaticojejunostomy is done for types I and II.
5. Supportive therapy with fat and water-soluble vitamins is mandatory for management in neonatal cholestasis. In PFIC and Alagille syndrome, pruritus must be managed medically or surgically.

MORE ON THIS TOPIC

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Table 5 Clinical features, investigations, treatment and outcome of children with progressive familial intrahepatic cholestasis

Clinical parameters	PFIC1	PFIC2	PFIC3
Onset*	Infancy	Neonatal age	Adolescence Rarely infantile period
Rate of progression	Moderate	Fast	Slow
Cirrhosis	By 1st decade of life	By 1st year of life	Young adults
Extrahepatic [†] manifestations	Present	None	None
GGT	Normal or low	Normal or low	High
Serum cholesterol	Normal	Normal	Normal or elevated
Serum primary bile acids	Very high	Very high	High
Bile composition	Low primary bile acid (3–8 mM)	Very low primary bile acid (<1 mM)	Low phospholipid 1–15% total (N = 19–24%)
EM of bile	Coarse granular bile (Byler's bile)	Amorphous bile	-
Liver histology	Bland cholestasis	Giant cell hepatitis	Ductular proliferation
Immunostaining	Nonspecific	BSEP immunostaining absent	MDR3 protein immunostaining absent
Gene protein	ATP8B1 (FIC1)	ABCB11 (BSEP)	ABCB4 (MDR3)
Treatment [@]	Supportive Biliary diversion	Supportive Biliary diversion LT	Supportive LT

Abbreviations: GGT, gamma-glutamyl transpeptidase; EM, electron microscopy; LT, liver transplant; PFIC, progressive familial intrahepatic cholestasis.

*Pruritus, the dominant presentation in PFIC manifests after 4 months of age as the child does not develop hand motor coordination till then. Generalized irritability and constant rubbing against mother's clothes are early signs of the same. Initially child learns itching around ears and face and then in the rest of the body as the child grows up. Jaundice and nutritional deficiencies (fat and fat soluble) are other manifestations.

[†]Diarrhea, pancreatitis, sensorineural deafness and wheeze are the extrahepatic. manifestations.

@Treatment of PFIC:

- Supportive: Ursodeoxycholic acid (UDCA), and management of pruritus.
- Biliary diversion procedures are done in intractable pruritus with poor quality of life before the development of cirrhosis. It has 75% clinical and biochemical response.
- Diversion procedures are: partial external (jejunal conduit draining gallbladder to external surface of abdominal wall), partial internal (gallbladder to colon) and ileal bypass.
- LT is offered in end-stage liver disease. In PFIC1, LT is discouraged as diarrhea persists even after LT due to the receptor defect in intestine.

Table 6 Supportive management of neonatal cholestasis

Nutrition: 85% of fat must be given as medium chain triglycerides in a total requirement of 120–140 kcal/kg/day		
Drug	Dose	Side effects
Vitamin K	2.5–5 mg on alternate day (available as oral or parenteral)	None
Vitamin D (cholecalciferol, 25-OH cholecalciferol)	2,500–5,000 IU/day 3–5 µg/kg/day	Hypercalcemia Nephrocalcinosis
Vitamin A	Aquasol A: 2,500–5,000 IU/day or Injectable: 30,000 IU IM at diagnosis and then 10,000 IU monthly till cholestasis resolves	Hepatotoxicity Pseudotumor cerebri Hypercalcemia
Vitamin E	Aquasol E: 50–400 IU/day	Diarrhea
Water-soluble vitamins	Twice the recommended daily allowances	None
Pruritus		
UDCA	10–20 mg/kg/day	Diarrhea
Rifampicin	10 mg/kg/day	Hepatotoxicity
Cholestyramine	0.25–0.5 g/kg/day	Steatorrhea, constipation

Chapter 37.4

Portal Hypertension

Surender Kumar Yachha, Moinak Sen Sarma

The superior mesenteric vein (SMV) and splenic vein (SV) join to form the portal vein which constitutes 80% of blood supply to the liver, rich with nutrient and hormones from the gut. Very low resistance in the portal bed results in low baseline pressure. Portal hypertension (PHT) is defined as an elevation of portal blood pressure above 5 mm Hg. It is one of the major causes of morbidity and mortality in pediatric liver diseases.

NORMAL PORTOSYSTEMIC ANASTOMOSES

The portal system begins as capillaries which originate in the mesentery of the intestines and spleen and end in the hepatic sinusoids. SMV drains venous blood from entire small bowel and mid-transverse colon. Inferior mesenteric vein (IMV) drains blood from mid-transverse colon to rectum. IMV joins SV proximal to its junction with SMV. Splenic vein joins the SMV to form portal vein, which enters the liver and gives off right and left branches.

Short gastric veins and posterior gastric vein drain fundus of stomach into SV. Left gastroepiploic vein drain the anterior and posterior surfaces body of stomach along the greater curvature to drain into SV. Right gastroepiploic vein drains the distal part of stomach and antrum along greater curvature into the SMV. Left gastric vein (coronary vein) drains upper part of body along lesser curvature, fundus and lower part of esophagus to join the portal vein just before it gives off its intrahepatic branches. Right gastric vein drains the lower part of body along lesser curvature and pylorus to drain into the portal vein also.

PATHOPHYSIOLOGY

Portal hypertension occurs due to two main reasons: extrahepatic portal venous obstruction (EHPVO) and cirrhosis. PHT is the result of a combination of increased portal resistance and/or increased portal blood flow. The mechanism of the increased portal resistance depends on the site and cause of PHT. Pressure is directly proportional to both blood flow through the portal system and resistance to the blood flow (Ohm's Law). Resistance in turn is inversely related to the radius of the lumen raised to the fourth power (Poiseuille's law). Hence, small changes in the vasculature may result in large changes in pressure. Blood viscosity and vessel length also can influence resistance. In cirrhosis, in an attempt to nourish the compromised hepatic parenchyma there is an increase in portal venous flow by vasodilatation in the splanchnic circulation that is mediated by increased nitric oxide (NO) production.

In EHPVO, the event of an acute portal venous thrombosis (PVT) is usually unrecognized and may have occurred due to a known or unknown etiology. The child may have had a preceding febrile illness, intra-abdominal infection or dehydrating illness followed by subtle abdominal pain or transient ascites which may have been forgotten or undetected. In retrospect, a search into the child's past history is often unyielding and perplexing for the physician. Following this event of PVT, the thrombus begins to organize. In order to bypass the obstruction, multiple hepatopetal collaterals form in 6–20 days to compensate for the high volume blood flow from the splanchnic system draining into the liver. A well-established portal cavernoma forms in 3 weeks. Portal cavernoma is a radiological term that denotes the replacement of the portal vein with a bunch of collaterals having blood flow toward the liver.

In order to decompress the portal system, collaterals and spontaneous shunts form that connects the high-pressure portal venous system with lower-pressure systemic veins. Collaterals develop by dilatation of existing dormant collateral vessels, as well as development of new blood vessels and sprouts (angiogenesis) mediated by increased NO and endothelin-1. Unfortunately, this process of angiogenesis and collateralization is insufficient for normalizing portal pressure and actually causes complications of PHT, such as varices and hemorrhoids. Chronic back pressure from the portal system causes congestion and enlargement of spleen.

Anatomical Changes in Portal Hypertension

- To bypass the obstruction, there is dilatation of portal venous tributaries and reversal of blood flow in these veins that anastomose with the systemic veins.
 - Valves of the perforators connecting the portal to systemic circulation become incompetent and dilated submucosal plexus develops which are known as varices. *See details below.*
 - There are also embryonic channels that are normally obliterated and open up in PHT. A typical example of the same is paraumbilical veins that exist normally between left branch of PV and coronary vein.
 - Formation of new collaterals in abdomen. *See details below.*
- Portosystemic circulation and its changes in PHT are shown in **Figure 1** and **Table 1**.

Varices

Varices are abnormally tortuous vessels in the venous system most commonly seen in esophagus and stomach. Hepatic venous pressure gradient (HVP) an indirect marker of the portal pressure is calculated by difference between the wedged hepatic venous pressure (WHVP) and free hepatic vein pressure (FHVP). Varices usually form and rupture when HVP is greater than 10 mm Hg and greater than 12 mm Hg respectively. They rupture when the intravariceal pressure increases and exceeds the variceal wall strength. High blood flow and lack of natural mechanisms for tamponade may result in life-threatening hemorrhage. Rarely, varices may bleed at ectopic locations (duodenum, small bowel, colonic) or be present around the extrahepatic biliary tract leading to complications.

Collateral Flow

In intrahepatic PHT, the reopened paraumbilical vein communicates with the left branch of the portal vein to the anterior abdominal walls (superior and inferior epigastric veins) which finally drain into the IVC through iliac veins bypassing the liver. The direction of flow of the veins above and below the umbilicus is away from the same towards the periphery. Caput medusa (radiating tortuous vessels from the umbilicus appearing as a bunch of snakes) is an exaggerated form of this exuberant portosystemic collateralization. An audible venous hum, the Cruveilhier-Baumgarten murmur, may occasionally be appreciated through these vessels. Both these features are rare in children.

In extrahepatic PHT, the main portal vein and invariably its left branch are occluded, so dilated veins do not appear on anterior abdominal wall.

In Budd-Chiari syndrome associated with an inferior vena cava block, the collateral venous circulation is established via the lumbar veins that connect the superior epigastric, inferior epigastric and circumflex iliac to the drain through tributaries of azygos and hemiazygos vein which finally drains into the superior vena cava. The direction of flow of anterior abdominal wall veins is cephalad both above and below umbilicus. Flank veins and tortuous back veins are essential of this entity.

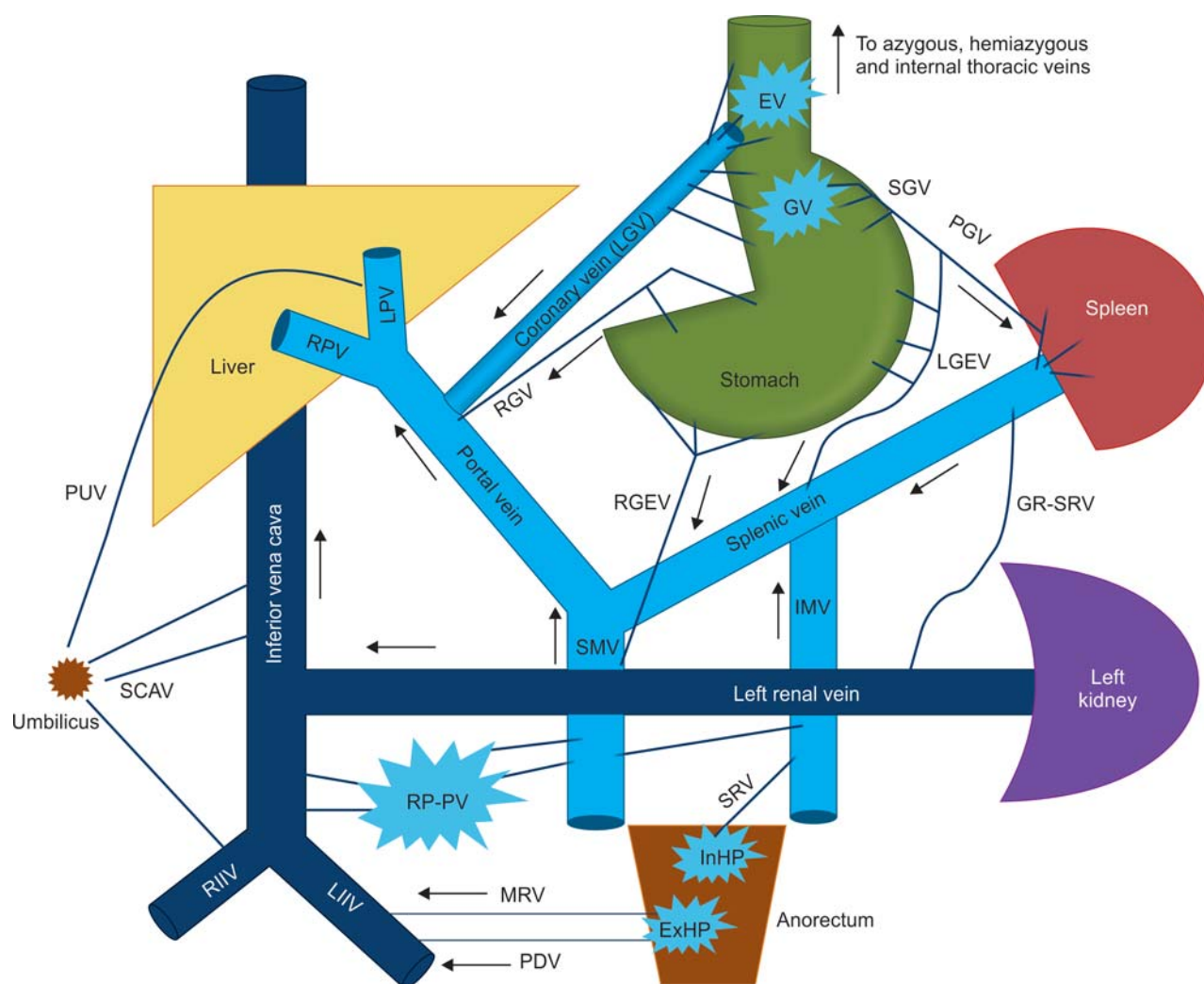


Figure 1 Schematic representation of portosystemic circulation

Abbreviations: RPV, Right branch of portal vein; LPV, left branch of portal vein; EV, esophageal varices; GV, gastric varices; SGV, short gastric veins; PGV, posterior gastric vein; LGV (coronary vein), left gastric vein; RGV, right gastric vein; LGEV, left gastroepiploic vein; RGEV, right gastroepiploic vein; GR-SRV, gastrosplenic vein; IMV, inferior mesenteric vein; SMV, superior mesenteric vein; RP-PV, retroperitoneal-paravertebral venous plexus; SCAV, subcutaneous anterior abdominal wall veins; PUV, paraumbilical vein; MRV, middle rectal vein; PDV, pudendal vein; InHP, internal hemorrhoidal plexus; SRV, superior rectal vein; RIIV, right internal iliac vein; LIIV, left internal iliac vein. Red arrows indicate the direction of normal blood flow. NB: The normal flow is reversed in the gastrosplenic circuit.

Table 1 Effects of portal and systemic venous communication in portal hypertension

Communication with portal circulation	Communication with systemic circulation	Effects
Left gastric and lower esophageal veins	Lower branches of esophageal veins that drain into azygos and hemiazygos veins	Esophageal and gastric varices*
Superior rectal veins	Middle and inferior rectal veins drain into internal iliac and pudendal veins	Rectal varices
Persistent tributaries of left branch of PV	Periumbilical branches of superior and inferior epigastric veins	Caput medusae
Intraparenchymal branches of right branch of PV in bare area	Retroperitoneal veins that drain into lumbar, azygos and hemiazygos	Retroperitoneal plexus (at risk during intervention procedures and surgeries)
Omental and colonic veins in the region of hepatic and splenic flexure	Retroperitoneal veins that drain into lumbar vein	Rarely retroperitoneal plexus forms in these regions

*Gastric varices are formed by another pathway. Due to reversal of blood flow in the splenic vein, afferents from short and posterior gastric veins draining the fundus will enlarge into a varix in the fundus. This will drain through gastrosplenic shunt into the left renal vein.

HOW TO CLINICALLY SUSPECT PORTAL HYPERTENSION?

Extrahepatic Portal Hypertension

- Splenomegaly with upper gastrointestinal (UGI) bleeding
Or
- Moderate to large splenomegaly (without bleeding).

Intrahepatic Portal Hypertension

Splenomegaly ± UGI bleeding with one or more of the following:

- Presence of ascites
- Abdominal veins
- Any other evidence of liver disease (jaundice, encephalopathy, stigmata of cirrhosis or abnormal LFT).

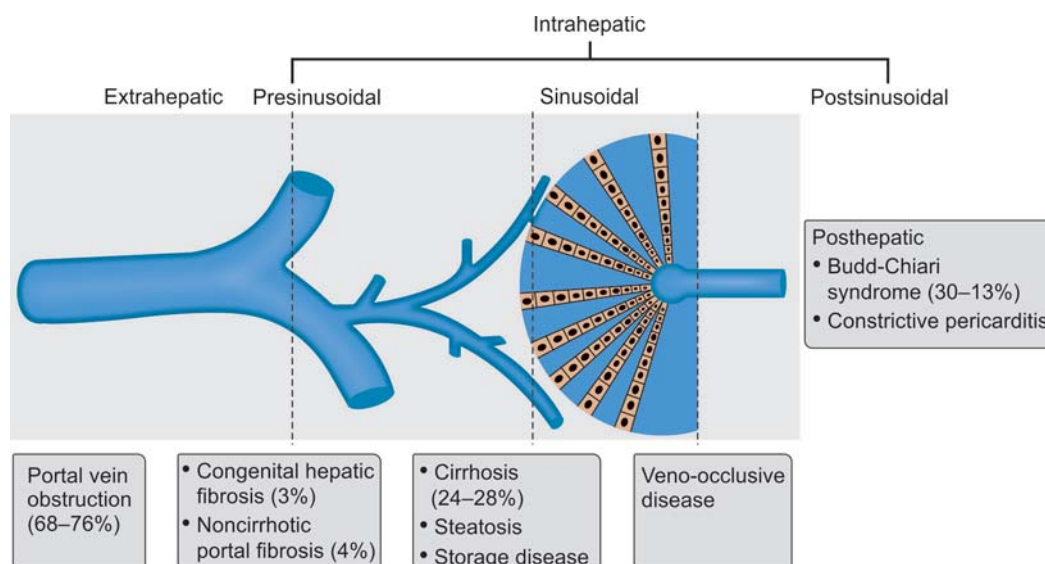


Figure 2 Common causes of portal hypertension in children

Common causes, investigations and complications of PHT are shown in **Figure 2**, **Box 1**, and **Table 2**.

BOX 1 Mandatory tests in portal hypertension

- Hemogram for hypersplenism
- Liver function tests including prothrombin time
- Doppler-ultrasound:
 - Portal cavernoma and patency of SV, SMV, IMV and left renal vein
 - Portal vein diameter
 - Hepatic veins and IVC patency
 - Changes of cirrhosis in liver
 - Changes in biliary tract (extrahepatic and intrahepatic biliary dilatation)
- UGI endoscopy for varices
- Specific investigations of underlying etiology

EXTRAHEPATIC PORTAL VENOUS OBSTRUCTION

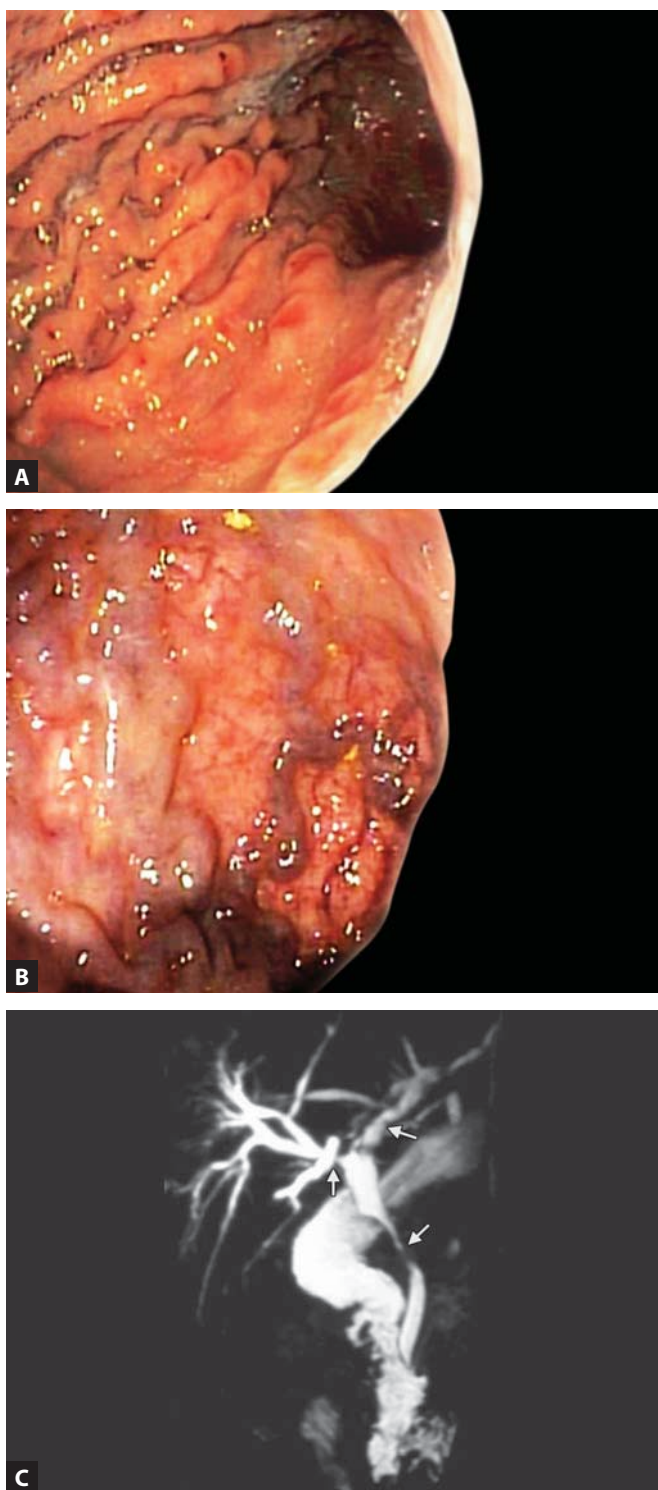
This disorder predominantly occurs in children with its onset occurring and manifesting sometime during childhood followed by its persistence throughout adolescence and into adulthood. Major bulk of PHT in Indian children is due to EHPVO in contrast to cirrhosis in the West. EHPVO is the consequence of PVT just outside the liver. It may have variable extension proximally into the intrahepatic radicles, distally into its confluence, tributaries (SV and SMV) or entire splanchnic system. Isolated involvement of the splenic, superior mesenteric or IMV is not included under the definition of EHPVO. For the working definition of EHPVO, it is mandatory to document a portal cavernoma on imaging.

Etiopathogenesis

What exactly causes PVT is not clearly known. Intra-abdominal infections produce endotoxemia that result in portal vein

Table 2 Complications of portal hypertension

Effects	Comments
Hypersplenism	Sequestration from long-standing splenomegaly. Usually asymptomatic clinically. Decrease of ≥ 2 cell lines (total leukocyte $< 4,000/\text{mm}^3$ and platelet counts $< 50,000/\text{mm}^3$). Anemia may be confounding (recent or chronic bleeding).
Portal hypertensive gastropathy (PHG) and duodenopathy (Fig. 3A)	Mucosal changes in stomach and duodenum due to chronic congestion. Milder forms of PHG appear as snake skin-like changes on endoscopy. Severe forms of PHG have red spots over the same which uncommonly bleed. Watermelon-like appearance in the antrum is known as gastric antral vascular ectasia (GAVE).
Portal colopathy (Fig. 3B)	Seen in long-standing portal hypertension. Asymptomatic in majority. Present infrequently as painless rectal bleed. Large anorectal varices and/or mucosal changes (hyperemia, ectasias, superficial ulcers) are demonstrated on colonoscopy.
Portal biliopathy (Fig. 3C)	Formation of varices around the bile duct (epicholedochal and paracholedochal) and gallbladder. Seen in long-standing portal hypertension. Compression or ischemia of bile duct by varices and bile flow stasis lead to stricture and stone formation in biliary tract. Usually asymptomatic in the majority. Symptomatic in 10–20% of adolescents and adults as cholestatic jaundice with episodes of cholangitis. Diagnosed on cholangiography and/or endoscopic ultrasound.
<i>Additional complications in patients with cirrhosis</i>	
Ascites	Pathophysiology and management detailed in Section 35, Chapter 35.20.
Hepatic encephalopathy	Refer to Chapter 37.10 for details.
Hepatopulmonary syndrome (HPS)	Portosystemic shunting causes decreased vasodilator (NO and endothelin) clearance in the liver which further leads to right-to-left shunting and ventilation-perfusion mismatch in the alveoli. Manifests as insidious onset dyspnea (orthopnea), cyanosis and clubbing.
Hepatorenal syndrome	PHT leads to activation of renin-angiotensin-aldosterone system, renal vasoconstriction and impaired renal function. Manifests as prerenal failure (anuria and azotemia nonresponsive to diuretics or albumin). Often precipitated by spontaneous bacterial peritonitis, large volume paracentesis or GI bleed in a cirrhotic. Rarely observed in children.



Figures 3A to C (A) Portal hypertensive gastropathy; (B) Anorectal varices (portal colopathy); (C) Narrowing of common bile duct with upstream biliary dilatation, narrowing of right hepatic duct and irregular dilation of left hepatic duct suggestive of portal biliopathy

phlebosclerosis is one of the postulations. Various studies have shown that intra-abdominal sepsis, umbilical sepsis, umbilical catheterization and *Bacteroides* bacteremia are the causative agents of portal phlebitis. Studies have failed to show any pre-

existing hypercoagulable states in children. Rarely, congenital anomalies of portal vein and iatrogenic trauma during surgery have been reported.

Clinical Presentation

Almost 85% of children present with upper gastrointestinal bleeding due to variceal hemorrhage (most commonly esophageal varices). The rest 15% may present as nonbleeders with only splenomegaly (**Figs 4A and B**). The duration from the development of PHT to clinical manifestations is highly variable. Bleeders may manifest from anytime in infancy to adulthood. Mean age of presentation is 6.3–9.3 years with a mean number of 1.8–3.1 bleeding episodes per child.

Preceding variceal bleeds, there is often a history of febrile illness and concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs) inducing erosions superimposed on pre-existing portal hypertensive gastropathy changes precipitating bleeding. Abdominal pressure from coughing in respiratory tract infection coupled with high cardiac output in fever make them prone for hemorrhage. Variceal bleeds in EHPVO are large volume well-tolerated bleeds necessitating the requirement of packed cell transfusion. Presence of gastrointestinal (GI) bleeding and absence of jaundice are 97.5% accurate in predicting the diagnosis of EHPVO. Clinical examination reveals splenomegaly with no evidence of chronic liver disease. The size of the spleen may decrease acutely just after a massive bleeding to compensate for the volume loss. Dragging sensation and left upper quadrant pain may occur due to large size of spleen. Splenic infarction is a complication in long-standing EHPVO children with massive splenomegaly (**Fig. 4C**).

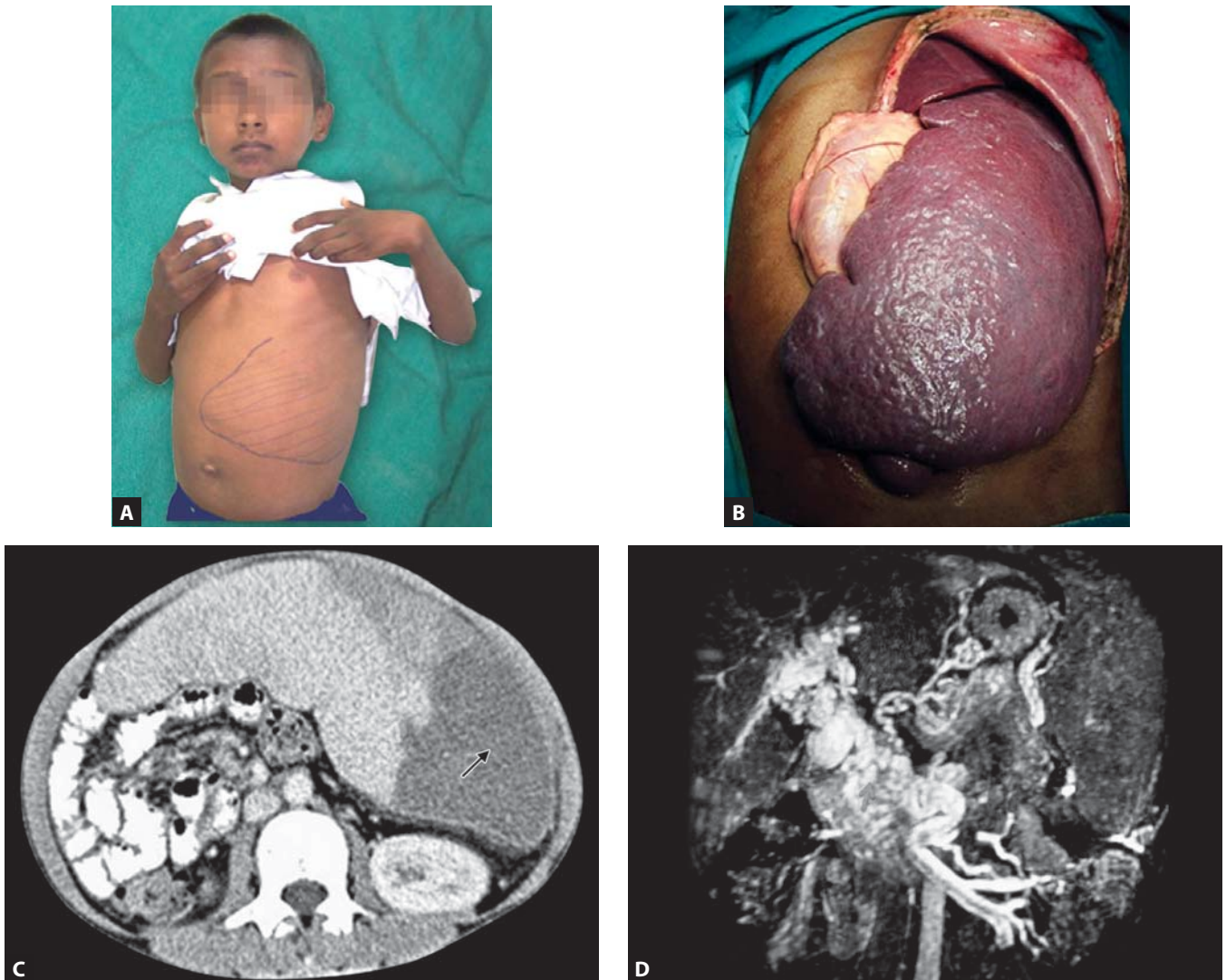
Rarely, after a massive bleed, there may be transient transudative ascites that quickly resolves with diuretics (in contrast to a cirrhotic with recurrent history of ascites with or without antecedent bleed followed by aggressive, prolonged diuretic therapy). There are a few situations in which jaundice may be present in EHPVO particularly due to portal biliopathy. Mild icterus and biochemically unconjugated hyperbilirubinemia may be seen due to increased hemolysis in the enlarged spleen. Unscreened blood transfusion in the past may cause chronic hepatitis B or C infection manifesting later with conjugated jaundice. Most importantly jaundice is a manifestation of portal biliopathy-related changes as detailed in the chapter.

Growth Retardation and Quality of Life

Duration of PHT determines the growth of the child. Growth retardation (stunting and wasting) occurs in up to 54% children. The theories proposed for the same are: (1) malabsorption due to portal enteropathy; (2) deprivation of hepatotropic factors due to poor portal supply to liver; (3) chronic anemia; and (4) growth hormone resistance and low insulin like growth factor (IGF). Chronic dragging sensation and apprehensions of rupture of a massive spleen may preclude them from contact sports. Children with EHPVO have a poor quality of life (QOL) in physical, emotional, social and school functioning health domains. Increasing size of spleen, presence of hypersplenism and growth retardation significantly affects the QOL. A trend in improvement of QOL is seen after shunt surgery.

Investigations

Doppler ultrasonography is the best noninvasive investigation for diagnosis of EHPVO. Portal cavernoma on ultrasound confirms EHPVO. Portal vein block is seen in 92% cases and other 8% may have total splenoportal axis block. The Doppler ultrasonography is sensitive (94–100%) and specific (96%) to diagnose EHPVO.



Figures 4A to D (A) Massive splenomegaly in a boy with EHPVO; (B) Congested large spleen seen at surgery; (C) CT scan showing splenic infarct; (D) Portal cavernoma seen on MR portovenogram

Doppler also gives additional information about the degree of splenomegaly, size of SV and left renal vein, patency of SMV and IMV, presence of ascites and portosystemic shunts particularly for surgical intervention. CT angiography or MR portovenogram is indicated in cases where Doppler has been inconclusive and as a definitive road-map before contemplating shunt surgery in select cases (**Fig. 4D**).

The liver function tests in EHPVO are essentially normal. Hypoalbuminemia may occur during bleeding episodes. Blood counts may reveal hypersplenism. At initial evaluation serological tests for hepatitis B and C infections should be done in patients who have received blood transfusion before the start of endoscopic therapy. All patients of EHPVO, negative for hepatitis B infection should be immunized.

CIRRHOSIS IN CHILDREN

Presentation of cirrhosis is variable ranging from asymptomatic to decompensated disease. As cirrhosis advances, eventually the clinical picture evolves into jaundice and PHT. Decompensation

is heralded with the development of edema and ascites due to hypoalbuminemia, encephalopathy due to hyperammonemia and/or bleeding (variceal or coagulopathy). **Table 3** lists the common causes of cirrhosis (sinusoidal PHT) in children.

Clinical Manifestations

History of recurrent or persistent jaundice, ascites, coagulopathy or encephalopathy (one or more) favors the diagnosis of an underlying chronic liver disease. However, this history may be absent in majority as cirrhotic children usually have an insidious presentation with a smouldering course and overt features. In contrast to EHPVO, cirrhotics bleed less often. However, when they bleed, the hemorrhage is not well tolerated. It often worsens the child's condition further and results in decompensation that manifests as ascites and/or encephalopathy soon after the bleed. Cirrhosis may also be caused by extrahepatic biliary disease. Pruritus and cholangitis may be the manifestation. Examination of a cirrhotic child is summarized in **Table 4**. Investigations specific to cirrhosis are listed in **Table 5**.

MANAGEMENT OF PORTAL HYPERTENSION

Variceal Bleed

Flow charts 1 to 3 show the algorithms to manage variceal bleeding.

Most often, acute variceal bleeding occurs due to rupture of large esophageal varices. Gastric variceal bleeding is less frequent. Ongoing bleed is assessed by tachycardia, fall in blood pressure or postural drop (decrease in systolic blood pressure ≥ 20 mm Hg or a decrease in diastolic blood pressure ≥ 10 mm Hg within

Table 3 Common causes of cirrhosis (sinusoidal portal hypertension)

Infants and younger children (< 5 years of age)	Older children (> 5 years of age) and adolescents
Biliary atresia	Autoimmune liver disease
Choledochal cyst	Wilson disease
Progressive familial intrahepatic cholestasis I and II	Hepatitis B virus
Alagille syndrome*	Sclerosing cholangitis [#]
Galactosemia	Tyrosinemia type I
Tyrosinemia type I	Alagille syndrome*
Indian childhood cirrhosis	Progressive familial intrahepatic cholestasis III*
Glycogen storage disease IV	Niemann-Pick disease type C*
	Glycogen storage disease III*
	Nonalcoholic fatty liver disease (NAFLD)
	Choledochal cyst

*These are diseases beginning in the neonatal period or early infancy but have a slow progression. Cirrhosis and portal hypertension mostly manifest after the first decade.

[#]Sclerosing cholangitis may be intrahepatic, extrahepatic or both. Secondary causes (e.g., Langerhan's cell histiocytosis) are more common than primary (idiopathic) sclerosing cholangitis.

Hepatitis C-related cirrhosis develops in 5–20% of those infected and it takes 15–20 years for cirrhosis to develop. Hence, it is a rare cause of cirrhosis in children.

Table 4A General physical examination in a cirrhotic child

Features	Causes
Pallor	Bleed (GI, skin, intracranial), hemolysis (Wilson disease)
Icterus	Icteric tinge: early cirrhosis. Deep icterus: terminal disease, superimposed hemolysis or renal failure
Cyanosis	Hepatopulmonary syndrome (HPS)
Clubbing	HPS or intrapulmonary shunting
Edema	Pedal, facial, anasarca: feature of decompensation
Fat soluble vitamin deficiencies	Bitot spots, follicular keratosis (vitamin A), phrynoderma (essential fatty acids), rickets (vitamin D)
Skin changes	Paper-money skin (cirrhosis), pruritus scratch marks, vitiligo and psoriasis (autoimmune liver disease), acanthosis nigricans (NAFLD), xanthomas and xanthelasma (Alagille syndrome)
Ecchymoses	Vitamin K deficiency
Abnormal facies	Alagille facies: prominent forehead, deep-set eyes with moderate hypertelorism, pointed chin, and saddle or straight nose with a bulbous tip
Kayser-Fleischer ring	Wilson disease. (Mostly detected by slit-lamp examination. Rarely seen in naked eye examination)
Cataract	Galactosemia, Wilson disease
Vertical gaze palsy	Niemann-Pick disease

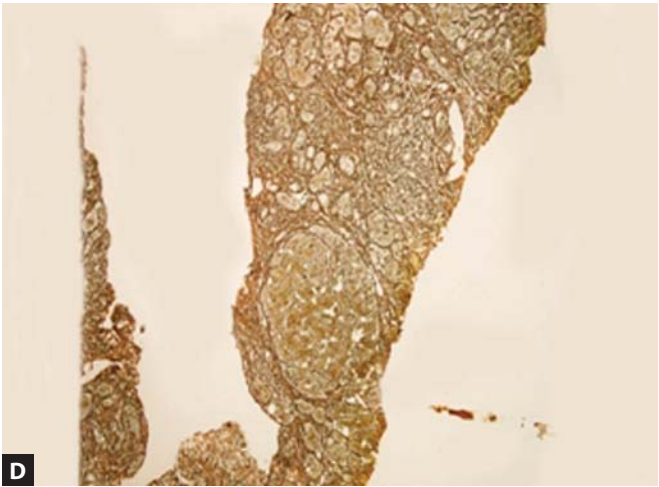
Table 4B Stigmata of chronic liver diseases (cirrhotics)

Features	Comments
Spider nevi	Small, raised, dark lesions with radially distributed convoluted vascular branches. Elicited by compression of the lesion in the center with a blunt end of a paper-pin. These are drained by the superior vena cava and are located in upper abdomen, axilla, neck and upper part of back. Cause: Increased estradiol in the circulation.
Palmar erythema	Physiological erythema may be normally seen up to 2 years of age. Relevant thereafter. Cause: Increased cardiac output or altered sex hormone metabolism (Fig. 5A).
Nail changes	Horizontal white bands (Muehrcke's nails) or leuconychia (Fig. 5B). Cause: Chronic malnutrition (hypoalbuminemia) in liver disease.
Sexual characteristics	Testicular atrophy in males, breast atrophy in females, loss of axillary or pubic hair. Rarely seen in adolescents. Cause: Altered sex hormone metabolism and reduced testosterone synthesis in liver.
Gynecomastia (males)	Usually bilateral. Unilateral gynecomastia occurs normally at puberty onset and may also occur due to spironolactone usage.

Paper-money skin and clubbing can also be accepted as stigmata of cirrhosis. Dupuytren's contracture and parotid enlargement are not usually seen in children and are specific for alcoholic cirrhosis in adults.

Table 4C Abdominal examination specific for cirrhosis

Features	Characteristics
Liver margins	Sharp and irregular (<i>Leafy</i> in Indian childhood cirrhosis).
Liver surface	Nodular, e.g., tyrosinemia, hepatitis B (postnecrotic macronodular cirrhosis).
Liver consistency	Firm is not specific for cirrhosis. Hard in congenital hepatic fibrosis.
Liver span	Shrunk specific for cirrhosis. Enlarged in cirrhosis due to secondary biliary causes, cholestatic diseases in infancy, storage disorders.
Differential enlargement	Left lobe larger than right lobe.
Splenomegaly	Mild-to-moderate. Massive in storage diseases.
Dilated tortuous veins	Sites: anterior abdominal wall, flank, back (Fig. 5C).
Ascites	Minimal: Puddle sign Moderate: shifting dullness Massive, tense: fluid thrill (shifting dullness absent)



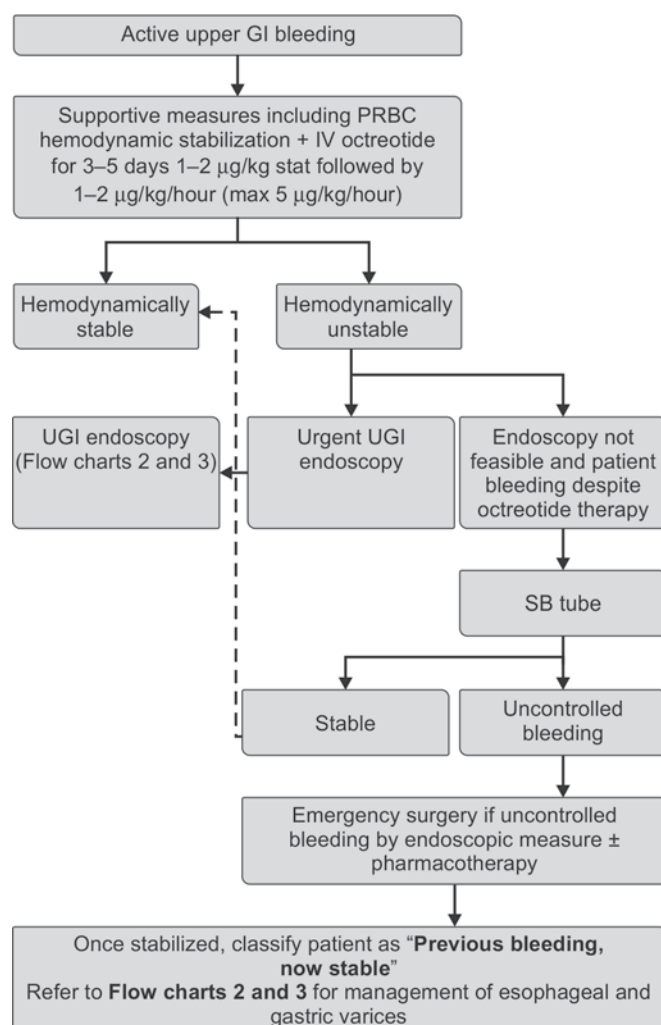
Figures 5A to D (A) Palmar erythema in a 10-year-old girl with autoimmune liver disease; (B) Leukonychia in an 8-year-old boy with Wilson disease; (C) Dilated anterior abdominal wall veins in a 2-year-old child with biliary atresia (failed portoenterostomy); (D) *Reticulin stain*: Bands of fibrosis forming nodules

Table 5 Investigations specific to cirrhosis

Investigations	Special features in cirrhosis
Liver function tests and prothrombin time	Hypoalbuminemia (< 3.5 g/dL) and coagulopathy (INR >1.5) indicate poor synthetic functions
Ultrasound Doppler	Liver margin irregularity and surface nodularity Caudate lobe hypertrophy Dilated PV with hepatofugal flow* Hepatic vein and inferior vena cava block in BCS Intrahepatic collaterals <i>Coarse parenchyma is not a definite evidence of cirrhosis</i>
Transient elastography (fibroscan)	Noninvasive measurement of degree of fibrosis Not required in all cases
Liver biopsy	Method: Percutaneous needle biopsy or transjugular (in select cases with persistent coagulopathy ± thrombocytopenia and necessary for histologic diagnosis) Loss of architecture, bands of fibrosis with nodule formation Masson's trichome or reticulin stain outlines the fibrosis (Fig. 5D) <i>Special features specific to underlying condition</i>

*Normal PV diameters (mm): Birth: 3–5, 1 year: 4–8, 5 years: 6–8, 10 years: 6–9, 15 years: 7–11.

In adults, PV diameter >13 mm is suggestive of intrahepatic PHT.

Flow chart 1 Management algorithm for active upper GI bleeding

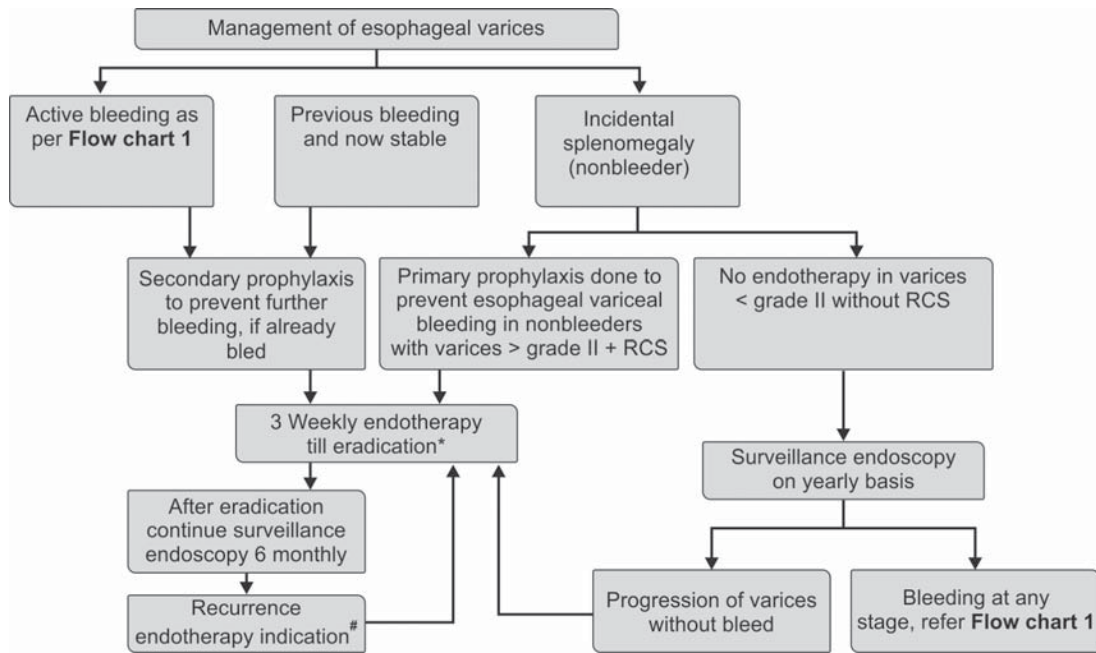
3 minutes of standing from supine position) and saline lavages. A wide bore nasogastric tube should be inserted and multiple cold saline lavages (250–500 mL each cycle) should be done till the effluent is clear. Lavages help to assess the ongoing bleed, reduce entry of blood (prevent hyperammonemia and encephalopathy in a cirrhotic) and help in clearance for visualization during UGI endoscopy. Hemodynamic resuscitation with packed cell transfusion and octreotide is to be followed by endoscopic therapy. Packed red cell transfusion should target to maintain hemoglobin at 8 mg/dL. Hypertransfusion may increase portal pressure and aggravate further bleeding from varices. In select settings pediatric Sengstaken-Blackmore tube is useful.

Octreotide is a somatostatin analog that decreases the splanchnic and azygos blood flow, thus reducing the pressure in the varices and also reduces the gastric secretion. Overall this therapy is well tolerated, with mild side effects like hyperglycemia, abdominal discomfort, nausea and diarrhea which often resolve spontaneously. Limited studies in children have shown control of bleeding in 64–71% children. Pediatric Sengstaken-Blakemore tube, a triple lumen tube has a limited role in the present era of effective endoscopic and pharmacotherapy.

Endoscopic Therapy

The goal of endoscopic management in bleeders is to find the cause, localize the site of bleeding and control acute variceal bleeding. Further, endoscopic procedures are done at intervals of 2–3 weeks. Eradication of esophageal varices to prevent rebleeding is called *secondary prophylaxis*. During endoscopy, one should look for the presence of esophageal varices, gastric varices, ectopic varices, portal hypertensive gastropathy and for any other cause of bleeding like duodenal or gastric ulcers. Prophylaxis to prevent the first episode of variceal bleed is called *primary prophylaxis*.

Grading of varices on endoscopy is given in **Box 2**. Various other classifications and grading systems are also available. Red-colored signs are markings on the surface of varices that make them at risk of bleed usually seen in esophageal varices greater than or equal to grade II. For secondary prophylaxis of esophageal varices, options are sclerotherapy alone or band ligation followed

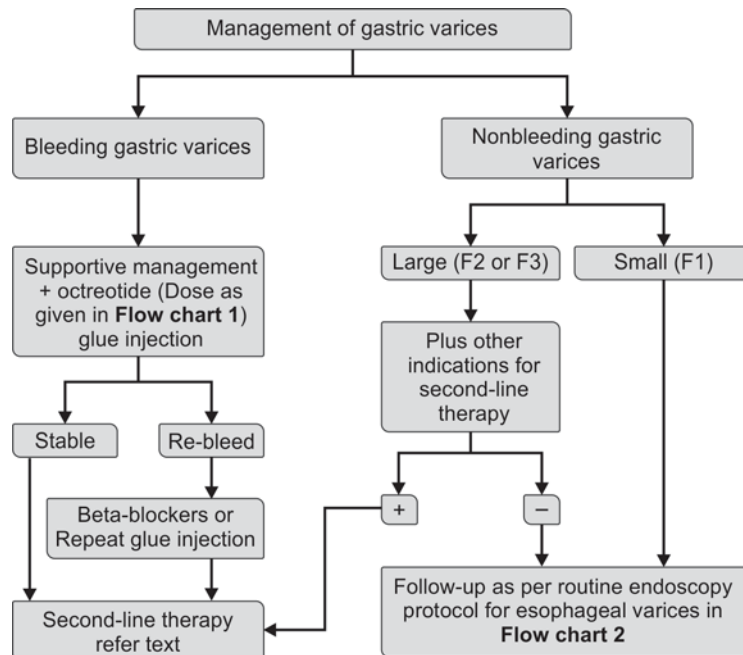
Flow chart 2 Management algorithm for esophageal varices

*EVL: Patient > 3 years of age; EST: Patients < 3 years of age or if bands are not affordable.

Initially, endotherapy is done with EVL for large varices followed by EST for smaller varices (not amenable to EVL) till they are eradicated.

#Endotherapy indication (EST/EVL): Only in esophageal varices grade II with RCS, Grade III or IV.

No endotherapy in varices < Grade II without RCS. Observe for progression, if there is recurrence but varices are small in size.

Flow chart 3 Management algorithm for gastric varices

by sclerotherapy till eradication. Options for primary prophylaxis, options are nonselective beta-blockers (NSBBs) or band ligation for varices greater than or equal to grade II (**Fig. 6A**) with red color signs. Small varices which are not at risk of bleeding may either be

observed or followed up with repeat endoscopies every 1–2 years and intervened when large. Bleeding gastric varices (IGV1, IGV2, GOV1, GOV2) are usually large (F2 or F3) (**Fig. 6B**) and are treated with glue injection followed by second-line therapy.

BOX 2 Grading of varices on endoscopy**Grade of esophageal varices (Paquet's classification)**

- I: Small varices without luminal prolapse
- II: Moderate sized varices showing luminal prolapse with minimal obscuring of gastroesophageal junction
- III: Large varices showing luminal prolapse substantially obscuring the gastroesophageal junction
- IV: Very large varices completely obscuring the gastroesophageal junction

Red color signs

Red wale marks: Dilated venules arranged longitudinally on the varices
Cherry red spots: Small red spots about 2 mm in diameter on the surface of the varices

Hemocystic spots: Round dark red blood blisters about 4 mm large in diameter

Diffuse redness: A diffuse red discoloration of the variceal surface

Location of gastric varices (Sarin's classification)

GOV1: Varices extending along the lesser curvature (continuing with esophageal varices),

GOV2: Varices extending along greater curvature (continuing with esophageal varices),

IGV1: Isolated varices in fundus (not continuing with esophageal varices),

IGV2: Isolated varices other than in fundus (elsewhere in stomach)

Size of gastric varices (Hashizume's classification)

F1: tortuous: F2: nodular: F3: tumorous

When classifying gastric varices both location and size should be taken into consideration

First-line Therapy for Variceal Bleeding

Endoscopic variceal ligation (EVL) is presently performed with a device called *multiple band ligator* (**Fig. 6C**). Varices are ligated sequentially in a spiral fashion which occludes them. Subsequently, superficial ulcers develop over the banded variceal site while the rubber band and necrotic ligated tissue sloughs off. Due to the size of the ligators, EVL can only be performed in children > 3 years of age and it is helpful to give sedation/general anesthesia so as to minimize the risk and increase the ease of performing the procedure.

When varices are large, EVL will rapidly downgrade the varices with fewer complications. Once the varices are smaller, endoscopic sclerotherapy (EST) is used to further downgrade the varices with advantages of blocking the perforators and paraesophageal collaterals to prevent recurrence.

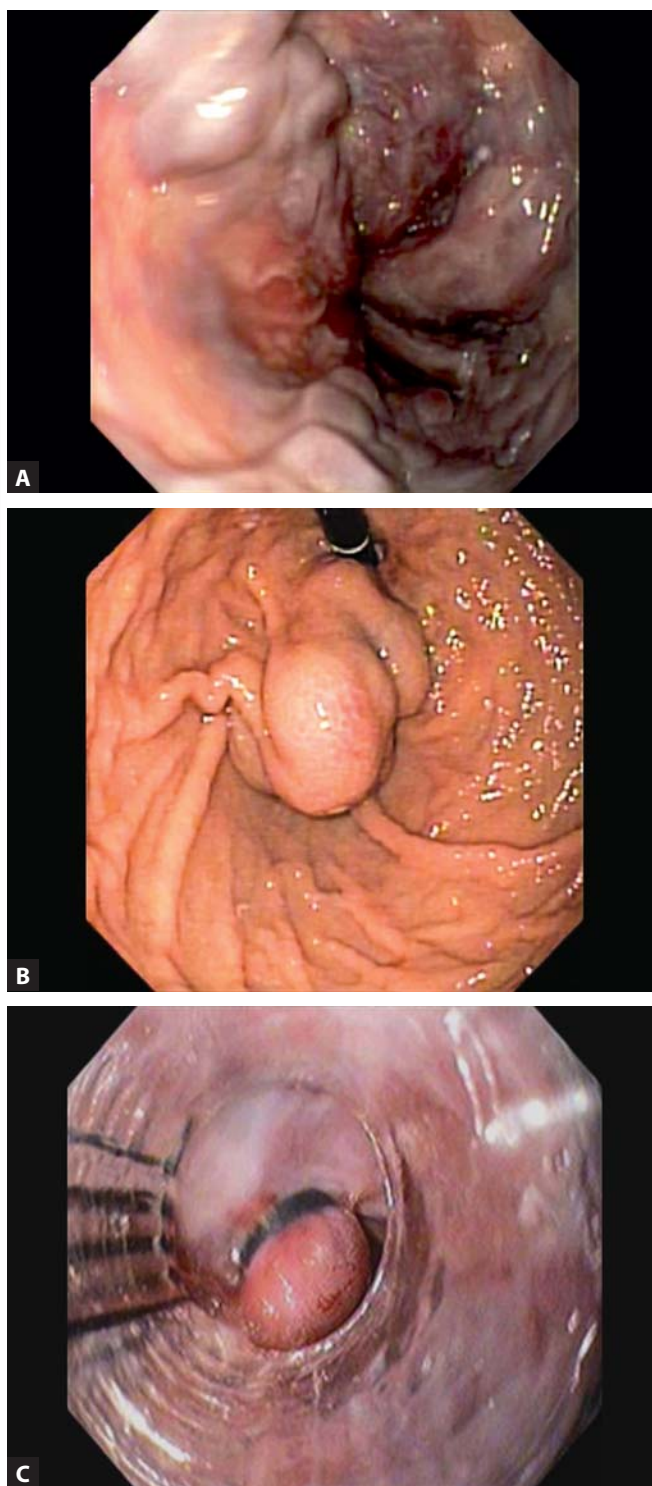
Sclerotherapy

Two to three milliliter of 1% ethoxysclerol is injected into the engorged vessel at various sites beginning 2–3 cm above the gastroesophageal junction. Endoscopic sclerotherapy (EST) is effective in more than 90% of cases in controlling esophageal variceal bleeding. Both the superficial varices as well as perforators are sclerosed. Transient fever and retrosternal discomfort are the commonest complaints postsclerotherapy and is observed in nearly a third of subjects. Major complications include esophageal ulceration (18–30%), perforation (1–1.4%), and later esophageal stricture (6–16%).

Following emergency EST or banding, the varices are then sclerosed at intervals of 2–3 weeks until all varices are obliterated (no varices) as shown in **Figure 6D**.

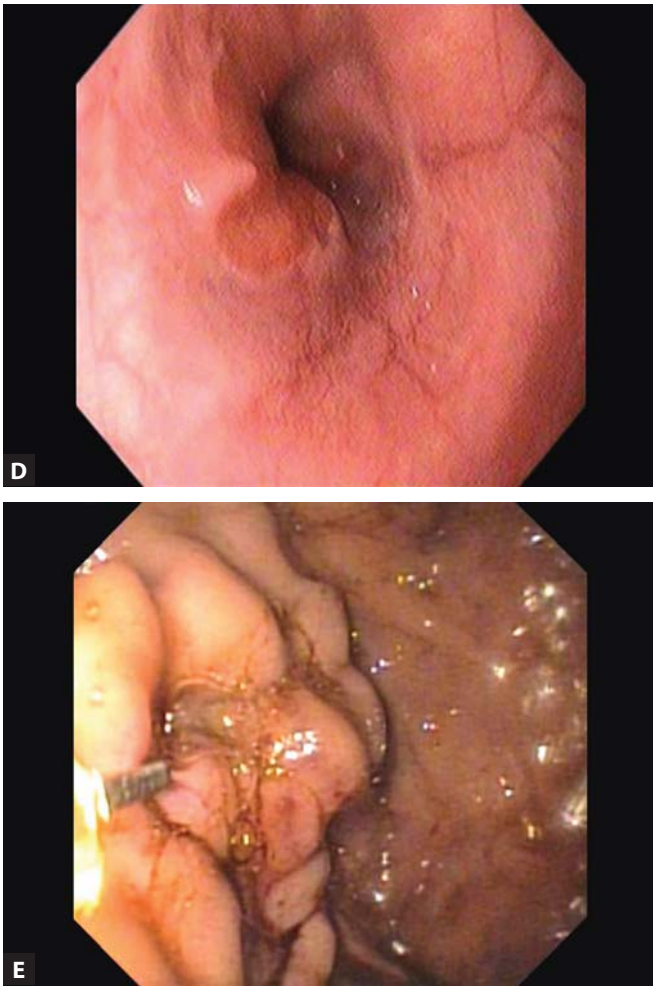
Glue Injection

The gastric varices are known to bleed more severely than esophageal varices, though the incidence of bleeding is much less. Endoscopic injection of the tissue adhesive (glue) N-butyl 2-cyanoacrylate or isobutyl 2-cyanoacrylate is used for gastric



Figures 6A to C (A) Large (grade IV) esophageal varices; (B) Large (F3) gastric varices; (C) Band ligation of esophageal varices

varices (**Fig. 6E**). These two agents are tissue adhesives that harden within 20 seconds of contact with blood, and result in more rapid control of active bleeding. Frequent glue injections are not advisable in children with EHPVO as it tracks into the tributaries and makes the anatomy nonshuntable in the future. After controlling acute gastric variceal bleed, it is advisable to do shunt surgery in EHPVO. However, in cirrhotic PHT shunt surgery is not indicated as it produces encephalopathy.



Figures 6D and E (D) Eradicated esophageal varices; (E) Glue injection of gastric varices

Beta-blockers

Beta-2 blockers cause blockade of the splanchnic bed, leaving unopposed α -adrenergic stimulation and thus decreased splanchnic and portal perfusion. Since β_1 -blockade lowers the cardiac output and portal perfusion, therapeutic doses (propranolol 0.5–2.0 mg/kg/day, maximum 8 mg/kg) should decrease the pulse rate by at least 25%, thereby reducing the HVPG less than 12 mm Hg. The major adverse effects associated with the use of propranolol are heart block, exacerbation of asthma. Long-term use may lead to impotence in 5%. In patients with diabetes mellitus, β -blockers should be avoided.

Second-line Therapy for Intractable Bleeding from Large Varices

Transjugular intrahepatic portosystemic shunt (TIPS) It is an emergency procedure where a catheter that introduced through the jugular into a hepatic vein. A needle tract through the hepatic parenchyma is created between the portal vein and hepatic vein and a stent is deployed. Thus, an *artificial portosystemic shunt* is created. In a cirrhotic, TIPS serves as a bridge to liver transplantation while on waiting list. Encephalopathy is particularly a problem with TIPS as the liver is bypassed and unfiltered toxins and ammonia from the gut reach the brain.

Balloon-occluded retrograde transvenous obliteration (BRTO) It is an emergency technique to embolize and give balloon tamponade to a bleeding gastric varix via a naturally available gastroduodenal

Table 6 Indications for shunt surgery in portal hypertension

Emergency	Elective
Acutely bleeding varices, failure of all conservative measures: <ul style="list-style-type: none"> • Pharmacotherapy (octreotide) • Sengstaken-Blackmore tube (rarely required in current era) and endoscopic management 	Complications of portal hypertension* <ul style="list-style-type: none"> • Large gastric varices (previously bled) • Portal colopathy • Portal biliopathy • Bleeding ectopic varices • Splenic infarction • Massive splenomegaly affecting quality of life • Symptomatic hypersplenism

*One or more of the complications. Each case needs to be individualized.

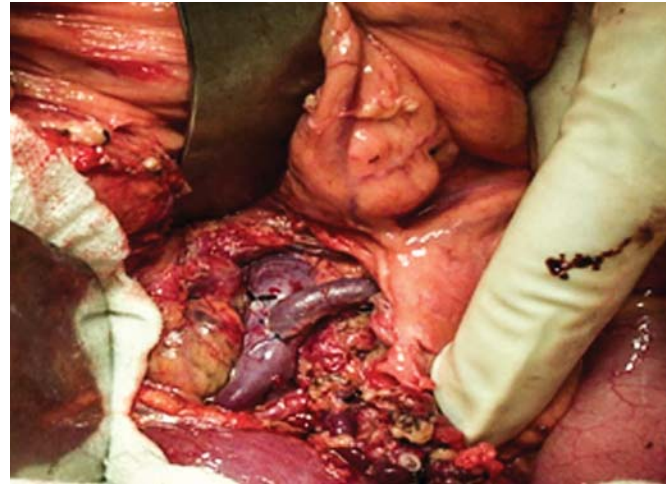


Figure 7 Central end-to-side splenorenal shunt surgery

shunt. The procedure can be done via transjugular or transfemoral routes. Limited procedures have been done in children so far.

Surgery In the pre-endoscopy era when EHPVO had high mortality, shunt surgery was the only treatment modality available. With the successful emergence of endoscopic procedures, shunt surgery are now a second-line therapy. Select indications in India are listed in **Table 6**. Shunt surgeries are mostly done for PHT in EHPVO common being central end-to-side splenorenal with splenectomy (**Fig. 7**), side-to-side splenorenal with spleen preserving and end-to-side mesocaval. However, shunt blocks may occur in 10% cases. Mesoportal Rex bypass (MPRB) is an example of a physiological (ideal) shunt where a graft is placed between the SMV and a patent left branch of PV through the Rex venous recessus, thereby restoring normal hepatopetal blood flow. This procedure is technically demanding.

Gastric devascularization for treatment of bleeding gastric varices is performed in a cirrhotic or in EHPVO having no suitable shuntable veins.

BUDD-CHIARI SYNDROME

Budd-Chiari syndrome (BCS) is a condition of hepatic venous outflow tract obstruction in the absence of cardiac and pericardial diseases.

Etiopathogenesis

Budd-Chiari syndrome (BCS) may be primary (idiopathic) or secondary (tumors and abscesses). Pathologically, there may be a thrombus in hepatic vein or inferior vena cava (IVC) or a membrane (web) in IVC. The site of block in children is predominantly hepatic vein (72–100%) followed by combined HV-IVC (24%)

and isolated IVC (4.3%). Prothrombotic states (factor V Leiden, proteins C or S deficiency, antiphospholipid antibody syndrome, myeloproliferative diseases) are significantly rare in children as compared to adults.

Clinical Presentation

Presentation ranges from complete absence of symptoms to fulminant hepatic failure, through acute (rapid) or chronic (progressive) development of symptoms over weeks to months before diagnosis is made. Hallmark of acute Budd-Chiari syndrome (20–30%) is tender hepatomegaly, and mild jaundice without significant encephalopathy. Chronic Budd-Chiari syndrome is most common (65%) manifesting as PHT with dilated venous collaterals. The ascites is tense and intractable that rapidly accumulates despite repeated large volume paracentesis and poorly controlled with diuretics. Often dilated tortuous veins with cephalad flow (above and below umbilicus) are seen in abdomen and flanks. Similar collaterals over back are the hallmark of an IVC obstruction. As chronic BCS is a *good cirrhotic*, there is usually absence of jaundice, near normal liver enzymes, low to normal albumin and absence of coagulopathy. GI bleed (35%) and pedal edema (22%) are relatively uncommon features. End-stage disease manifests just like any other cirrhotic with jaundice, shrunken liver, encephalopathy and coagulopathy.

Imaging

Color Doppler imaging and venography show thrombosis, narrowing of lumen or ostial block in the hepatic veins and/or IVC (**Fig. 8A**). Intrahepatic collateral and caudate lobe hypertrophy are the other features on Doppler ultrasound. Occasionally, a membrane may also be seen in IVC which is best demonstrated in combined antegrade and retrograde contrast cavography. Though liver biopsy is usually not required, the unique features are congestion and fibrosis in the centrilobular area.

Management

Table 7 summarizes the management of Budd-Chiari syndrome.

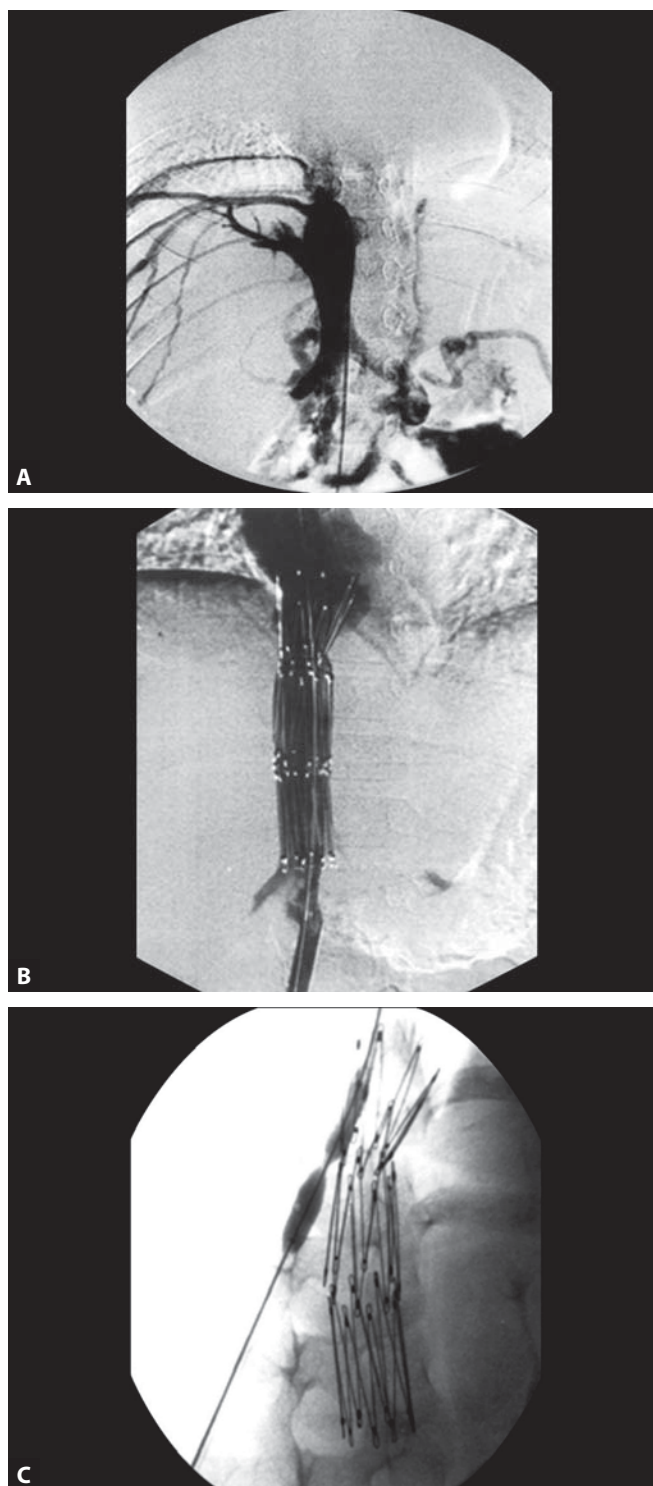
CONGENITAL HEPATIC FIBROSIS

During embryogenesis at 10th week, a double-layered structure known as *ductal plate* forms around the portal vein radicles, which proliferates to form the biliary tree. Ductal plate malformation (DPM) is the failed remodeling of the above that results in abnormally dilated biliary ductules. Congenital hepatic fibrosis refers to diffuse or segmental fibrosis of the liver due to DPM. In contrast to cirrhosis, liver architecture is preserved in congenital hepatic fibrosis.

Liver and extrahepatic involvement is summarized in **Table 8**. Majority (40–57%) present as well-tolerated variceal bleed with splenomegaly similar to EHPVO. In contrast, congenital hepatic fibrosis has a hard hepatomegaly with predominant left lobe. In a small proportion, recurrent episodes of jaundice occur during episodes of cholangitis due to biliary cystic disease that may progressively worsen the status of liver. Markedly elevated ALP or GGT (40–80%) with mildly raised or normal transaminases differentiates this condition from other causes of PHT. Hallmark of liver biopsy is DPM with broad bands of fibrosis and widening of portal tracts. Endoscopic eradication of varices, management of cholangitis and renal disease if present are the mainstay of therapy. Those without cholangitis or renal cysts are good candidates for shunt surgery and have a relatively favorable outcome.

NONCIRRHOTIC PORTAL FIBROSIS (HEPATOPORTAL SCLEROSIS OR IDIOPATHIC PORTAL HYPERTENSION)

This is a condition where there is neither cirrhosis nor extrahepatic portal obstruction but phlebosclerosis of the intrahepatic portal



Figures 8A to C (A) Blocked inferior vena cava seen on cavogram; (B) Stent placed in inferior vena cava; (C) Balloon angioplasty of right hepatic vein

radicles. Etiology is unclear but chronic exposure to vinyl chloride, copper sulfate or arsenic poisoning (West Bengal) has been postulated. The condition presents as massive splenomegaly in an adolescent or young adult with well-tolerated UGI bleed. The condition mimics EHPVO except that the portal vein is patent and dilated on imaging. Liver biopsy may be normal or shows obliterative portal venopathy. Nodularity of liver and ascites are rare features. Management is similar to EHPVO.

Table 7 Management of Budd-Chiari syndrome (BCS)

Control of ascites in all cases: Salt restriction, diuretics, large volume paracentesis		
Fulminant BCS	Acute BCS	Chronic BCS
Liver transplantation	Thrombolysis followed by radiological procedure See below	See below
Radiological intervention for ostial block/stenoses (preferably transjugular route than percutaneous transhepatic)		
<ul style="list-style-type: none"> Angioplasty ± stenting for short-length stenoses (< 5 cm length). Best is stenting if possible (Fig. 8B) TIPS for long segment stenoses (> 5 cm length) Long-term anticoagulation (warfarin) thereafter to prevent re-stenoses maintaining INR between 2.0 and 2.5 		
Membranous IVC		
<ul style="list-style-type: none"> Thin membranes: Intraluminal angioplasty by radiologic intervention (technically difficult) (Fig. 8C) Thicker membranes: Mesoatrial, cavoatrial or mesojugular shunts 		
Liver transplantation: Failure of all measures in acute or chronic BCS		

Table 8 Liver and extrahepatic involvement (including syndromes) in congenital hepatic fibrosis

Involvement	Condition
Liver involvement only	Isolated congenital hepatic fibrosis (most common) <i>Caroli's syndrome</i> : CHF + Caroli's disease (multiple cystic biliary dilatation)
Associated extrahepatic involvement	Autosomal recessive polycystic kidney disease (ARPKD) Nephronophthisis <i>Ivermark syndrome</i> : Pancreatic fibrosis <i>Joubert syndrome</i> : Dysgenesis of cerebellar vermis <i>Meckel-Gruber syndrome</i> : CNS and renal malformations <i>Bardet-Biedl syndrome</i> : Obesity, retinitis pigmentosa <i>Jeune syndrome</i> : Asphyxiating thoracic skeletal dystrophy <i>Congenital glycosylation disorder</i> : Protein losing enteropathy

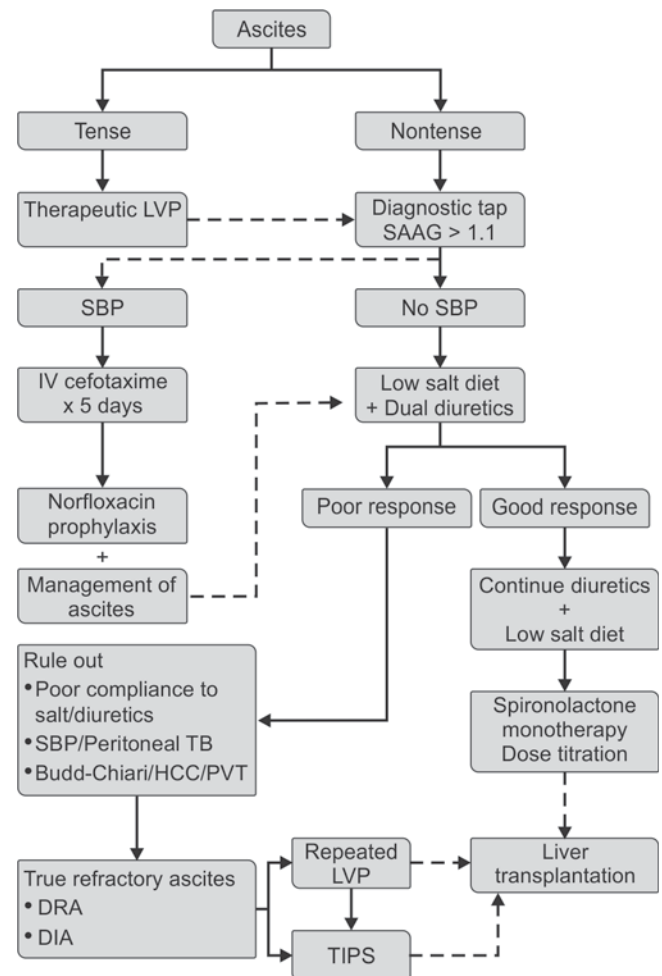
MANAGEMENT OF ASCITES

Ascites occurs in 44.1% and 12.8% children with cirrhosis and EHPVO respectively. Progressive deterioration of liver functions, PHT, splanchnic arterial vasodilatation and reduced plasma oncotic pressure due to low serum albumin all contribute to development of ascites. Inappropriate sequestration of fluid in splanchnic vascular bed leading to renin-angiotensin stimulation (underfilling theory) or primary inappropriate renal retention of sodium and water in the absence of volume depletion (overflow theory) are the other postulated mechanisms.

Management of ascites is detailed in a separate chapter in Section 35 on gastrointestinal disorders. **Flow chart 4** summarizes the approach for treating ascites.

Spontaneous Bacterial Peritonitis

Spontaneous bacterial peritonitis (SBP) is the most common complication of ascites occurring in 10–30% due to translocation of bacteria from the gut into peritoneal cavity. *E. coli*, *Klebsiella* and *S. aureus* are the most frequently isolated organisms. In a setting of ascites, presence of unexplained fever, abdominal pain, increased frequency of stools or worsening of encephalopathy in a cirrhotic should raise a suspicion for SBP. Frequently, SBP may be asymptomatic and incidentally detected on ascitic fluid analysis. Variants of SBP and their features are summarized in **Table 9**.

Flow chart 4 Management algorithm for ascites

Abbreviations: LVP, large volume paracentesis; SBP, spontaneous bacterial peritonitis; SAAG, serum ascites albumin gradient; dual diuretics (spironolactone and furosemide); HCC, hepatocellular carcinoma; PVT, portal vein thrombosis; TIPS, transjugular intrahepatic portosystemic shunt; DRA, diuretic resistant ascites (even after maximum dosage of both diuretics for at least 1 week); DIA, diuretic intractable ascites (side effects of diuretics appear before maximum doses can be tolerated).

Table 9 Description of spontaneous bacterial peritonitis and its variants

<i>Nomenclature</i>	<i>Ascitic fluid absolute neutrophil count/mm³</i>	<i>Ascitic fluid culture</i>	<i>Antibiotic treatment</i>
Spontaneous bacterial peritonitis (SBP) (monomicrobial neutrocytic)	> 250	Positive for single organism	Yes
Culture negative neutrocytic ascites (CNNA)	> 250	Negative	Yes
Monomicrobial nonneutrocytic bacterascites (MNB)	< 250	Positive	Yes if symptomatic No if asymptomatic

Table 10 Summary of portal hypertension: clinical features and investigations

	<i>Extrahepatic portal venous obstruction</i>	<i>Cirrhosis</i>	<i>Chronic Budd-Chiari syndrome</i>	<i>Congenital hepatic fibrosis</i>
GI bleed	Mostly (85%)	Rarely (20%)	± (35%)	± (40–50%)
Jaundice	Absent (unless complicated)	Recurrent or persistent (36%)	Absent (unless end stage)	Absent
Encephalopathy	Absent	± (30%) Recurrent	Absent (unless end stage)	Absent
Ascites	Absent (occasionally postbleed)	± (21%) Recurrent	Massive rapidly reaccumulating	Absent
Liver	Normal span	Shrunk or enlarged Irregular, nodular	Enlarged Irregular, nodular	Left lobe > right lobe Hard liver
Spleen	Enlarged	Enlarged	Enlarged	Enlarged
Dilated veins	None	Anterior abdominal wall Caput medusae	Abdominal wall Back veins in IVC block	±
LFT	Normal (unless complicated)	Abnormal	Near normal (unless end stage)	Normal except High ALP
Doppler USG	Portal cavernoma or block	Irregular liver outline Dilated PV	Hepatic veins ± IVC block	Irregular liver outline Left lobe enlarged
Collateral	Demonstration of varices in esophagus, and stomach by UGI	(seen in all three conditions, listed above)		

Treatment should be started empirically if SBP is suspected clinically, regardless of the availability of laboratory results. Antibiotic of choice is intravenous cefotaxime 50 mg/kg/dose every 8 hours for 5 days. This covers 95% of flora and is effective in 85% of cases. Risk factors for development of SBP are ascitic fluid protein concentration less than 1 g/dL, variceal hemorrhage and prior episode of SBP. Long-term administration of oral norfloxacin 5–7.5 mg/kg once a day in cirrhotic patients with ascitic fluid protein content of less than 1 g/dL or prior episode of SBP is recommended for prevention of SBP.

IN A NUTSHELL

1. A summary of portal hypertension (clinical features and investigations) is provided in **Table 10**.

MORE ON THIS TOPIC

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Chapter 37.5

Gastrointestinal Bleeding

Nishant Wadhwa

Hemorrhage in gastrointestinal (GI) tract can occur from a variety of sites and the etiologies can be equally diverse. The disorders causing GI bleeding can range from minor problems to severe life-threatening conditions. The first task is to ascertain whether bleeding is from the upper GI (UGI) or lower GI (LGI) tract.

UPPER VERSUS LOWER GASTROINTESTINAL BLEEDING

Gastrointestinal bleeding in children can arise from the UGI or LGI tract. *Hematemesis* refers to the vomiting of fresh red blood or of coffee-ground material and is suggestive of UGI bleeding from lesions proximal to the ligament of Treitz. *Melena* refers to the passage per rectum of tarry stools and denotes bleeding from the UGI tract or the proximal small bowel. The tarry stools may be intermingled with maroon or red blood. *Hematochezia* is the passage of bright red blood per rectum and indicates a source of bleeding low in the GI tract, usually in the colon. However, since blood exerts a cathartic action, massive UGI bleeding may occasionally present as hematochezia.

In some instances, caregivers or children may report *blood* in their stool or emesis when blood is actually not present. Certain foods and medications can alter the color of stool or vomitus and result in unnecessary diagnostic testing. These include food coloring, colored gelatin or children's drinks, red candy, beets, tomato skins, antibiotic syrups or melena (bismuth or iron preparations, spinach, blueberries, grapes, licorice). The widely available guaiac test is the currently recommended qualitative method for confirming the presence of gross or occult blood in vomitus or stool.

UPPER GASTROINTESTINAL BLEEDING

The child typically presents with hematemesis and melena. It is relatively uncommon but not rare. One prospective intensive care unit (ICU) study reported an incidence of 6.4% (63 episodes in 984 patients). Only four (0.4%) episodes were considered life-threatening. Other studies reported an incidence of 25% among ICU patients not receiving prophylactic therapy for bleeding. In an Indian study done at Sanjay Gandhi Postgraduate Institute of Medical Sciences (SGPGIMS), Lucknow, 75 children out of 139 had UGI bleeding out of which 95% were variceal bleeding. In another study done at Kashmir, 31% were variceal and 26% due to duodenal ulcers. Hematemesis may result from swallowed blood, UGI mucosal lesions, variceal bleeding, or rarely, hemobilia (hemorrhage into the biliary tract). Swallowed blood may be seen in conditions like epistaxis, sore throat, or breastfeeding

on cracked nipples or may follow dental work or tonsillectomy. Common causes of UGI bleeding in children are summarized in **Box 1**.

Approach to Upper Gastrointestinal Bleeding

A detailed history and careful physical examination accompanied by limited laboratory studies may identify the underlying cause and predict the severity of GI hemorrhage. A nasogastric tube aspirate should be obtained early in the evaluation to confirm the presence of fresh blood and to assess the extent of active bleeding. In a child, age-adjusted tachycardia is the most sensitive indicator of acute, severe blood loss. Hypotension and delayed capillary refill are ominous signs of severe hypovolemia and shock. The nasopharynx should be carefully examined to exclude a non-GI source of bleeding. Skin findings may reveal evidence of a generalized vascular disorder. Skin findings, such as a caput medusa, spider angiomas and jaundice may indicate liver dysfunction. Hemangioma and telangiectasia may be indicative of lesions in the GI tract. Cutaneous palpable purpuras are suggestive of Henoch-Schönlein purpura. The abdominal examination may reveal signs suggestive of portal hypertension (splenomegaly). Laboratory studies which are essential in the initial evaluation include baseline blood and platelet counts, coagulation profile and liver function test. The etiology of UGI bleeding in children can be varied in different age groups of patients (**Table 1**).

Common Causes of Upper Gastrointestinal Bleeding

Esophagitis

Severe gastroesophageal reflux disease in children who are suffering from neuromuscular diseases, cerebral palsy or hiatal hernia can present with bleeding as a result of ulcerating or

BOX 1 Common causes of upper gastrointestinal bleeding

- Swallowed blood
- Epistaxis, sore throat, breastfeeding, dental work or tonsillectomy
- Vitamin K deficiency in neonate
- Erosive esophagitis
- Mallory-Weiss tear
- Hemorrhagic gastritis: trauma, surgery, burns or severe systemic stress (patients in intensive care units)
- Reactive gastritis: nonsteroidal anti-inflammatory drug (NSAID) gastropathy, ingestion of caustic substances, stress, mechanical trauma, viral infection, Crohn's disease, vasculitis (Henoch-Schönlein purpura), radiation, bile reflux, bezoar, hiatal hernia, prolapse of the gastroesophageal junction, or congestive gastropathy (associated with portal hypertension)
- Peptic ulcer
- Variceal bleeding: associated with portal hypertension
- Submucosal masses: lipoma, stromal tumors, duplication
- Vascular malformation: angiodysplasia, hemangioma, Dieulafoy's lesion
- Hemobilia

Table 1 Age-wise etiological profile of upper gastrointestinal bleeding in decreasing order of frequency

Newborn	Infant	Older child
Swallowed maternal blood	Stress gastritis or ulcer	Mallory-Weiss tear
Vitamin K deficiency	Acid-peptic disease	Acid-peptic disease
Stress gastritis or ulcer	Mallory-Weiss tear	Varices
Acid-peptic disease	Vascular anomaly	Caustic ingestion
Vascular anomaly	Gastrointestinal duplications	Vasculitis (Henoch-Schönlein purpura)
Coagulopathy	Gastric/esophageal varices	Crohn's disease
Cows' milk protein allergy	Bowel obstruction	Hemobilia, Dieulafoy's lesion

erosive esophagitis. Other causes of bleeding esophagitis include mechanical injury from a foreign body, chemical injury from a caustic ingestion or medication (*pill esophagitis*) and infection [*Candida albicans*, *Aspergillus*, herpes simplex virus and cytomegalovirus (CMV)].

Ulcer and Gastritis

Gastric/duodenal ulcers and gastritis can be a cause of UGI bleeding usually in patients older than 1 year. Ulcers can occur secondary to stress from surgery, burns, increased intracranial pressure, birthing, acute self-limited viral illness and multiorgan system disease, medications, infection, ischemia, mechanical trauma from foreign bodies or gastrostomy tubes, and tumor. Stress gastritis and ulceration with secondary UGI bleeding are well recognized in the critically ill infant. Gastric ulceration and erosions may be seen in children receiving nonsteroidal anti-inflammatory drugs (NSAIDs). *Helicobacter pylori* infection can cause gastroduodenal ulcer disease in children; however, diffuse nodular gastritis is the commoner pediatric lesion. The nodules represent polyclonal mucosal lymphoid aggregates. Rarely there can be ulcerating gastric tumors in children include leiomyosarcoma, teratoma and hemangiopericytoma.

Variceal Bleeding

Gastroesophageal variceal bleeding occurs in portal hypertension secondary to intrahepatic or extrahepatic causes. Cirrhosis underlies varices in most affected adults, whereas in many pediatric studies, a large proportion of patients have extrahepatic portal hypertension with normal liver function. A study done at SGPGIMS showed that 87% of UGI bleeding is secondary to extrahepatic portal vein obstruction (EHPVO). Other extrahepatic venous obstructions, such as splenic vein thrombosis and hepatic vein obstruction (Budd-Chiari syndrome) can also cause variceal bleeds.

Cirrhosis as a cause of variceal bleed should be considered in children with chronic biliary diseases (biliary atresia, cystic fibrosis, sclerosing cholangitis) and chronic hepatocellular diseases. Noncirrhotic causes of intrahepatic portal hypertension in children are less common and include congenital hepatic fibrosis, veno-occlusive disease, and schistosomiasis.

Biliary atresia is the leading cause of pediatric liver failure. Survival requires early surgical intervention with portoenterostomy. Varices may form during infancy and early childhood despite appropriate therapy as a result of ineffective biliary drainage, chronic cholangitis, and progressive cirrhosis. The onset of bleeding relates to the rate of disease progression and can occur within the first year of life.

Other Causes

Vascular anomalies are a rare cause of UGI bleeding in children. They may be focal lesions, such as an isolated gastric hemangioma, Dieulafoy's lesion or diffuse lesions, such as hereditary hemorrhagic telangiectasia. Rarely GI duplications can occur in the UGI tract and cause hemorrhage. Other miscellaneous reports in children have included vasculitis (Henoch-Schönlein purpura) and gastric polyps. UGI bleeding in a newborn has been discussed in the section on Neonatology.

Diagnosis

Endoscopy

Esophagogastroduodenoscopy (EGD) is the preferred method to evaluate the UGI tract for a source of bleeding. Hematemesis is considered a *red flag* sign and is an indication for early EGD. The purpose of endoscopic examination in the patient with GI bleeding is to establish the diagnosis and treat the bleeding site if possible.

EGD can determine the source of bleeding in 90% of the cases. EGD is particularly useful in the diagnosis of mucosal lesions, such as gastritis, varices, esophagitis, peptic ulcers and Mallory-Weiss tears. Whenever esophageal/gastric variceal bleeding is suspected, EGD in the first 12 hours is usually recommended.

The risk of rebleeding can be assessed using the Forest classification (**Table 2**).

Other Modalities

Scintigraphy is rarely used to evaluate UGI bleeding. Technetium-labeled bleeding scans and sulfur colloid scans are helpful in the diagnosis of obscure bleeding in the small bowel. Angiography can be helpful in cases of massive UGI bleeding. Bleeding must be at least 0.5 mL/min to be detected by angiography. Angiography can also be used selectively in children when bleeding is so massive that endoscopic evaluation and therapy are difficult and when vascular anomalies or hemobilia are suspected. Apart from diagnosis, angiography also provides a therapeutic approach, such as the placement of *coils* for embolization of the bleeding vessel.

Plain radiography has a limited role in the diagnosis of UGI bleeding. A plain X-ray film is useful in identifying unsuspected foreign bodies, with free air suggesting bowel perforation and bowel obstruction. Ultrasonography is the modality of choice when liver disease, portal hypertension or large vascular anomalies are suspected. Structural information and blood flow dynamics can be assessed noninvasively and without the need for sedation by Doppler ultrasound. Computed tomography (CT) and magnetic resonance (MR) imaging are valuable noninvasive modalities when mass lesions or vascular malformations are suspected.

Treatment

The initial goal in the treatment of any child with UGI bleeding is to provide hemodynamic stability, to provide adequate oxygen delivery, fluid and blood resuscitation, and correction of any coagulopathy or metabolic/electrolyte abnormality. After initial stabilization, medical and endoscopic treatment can proceed so as to ascertain the exact etiology and institute appropriate specific therapy.

Medical Therapy

It comprises administration of proton pump inhibitors (PPIs) to increase the gastric pH and vasoactive drugs to reduce the splanchnic circulation.

Acid suppression is recommended in children with UGI bleeding, although studies to establish a benefit in this age group have not been performed. The studies in adults have examined the effect of acid suppression given before or after endoscopy (with or without therapeutic intervention). In the setting of active UGI bleeding due to peptic ulcers, high-dose antisecretory therapy with an intravenous (IV) infusion of PPI significantly reduced the rate of rebleeding compared with standard treatment in patients with bleeding ulcers.

Table 2 Forest classification for risk of rebleeding from upper GI tract

Endoscopic finding	Class	Risk of rebleeding
Clean base	III	Low
Hematin-covered flat spot	IIc	Low
Adherent clot	IIb	High
Visible vessel	IIa	High
Oozing hemorrhage	Ib	High
Spurting hemorrhage	Ia	High

Vasopressin is an effective agent to decrease splanchnic blood flow and thereby decrease GI bleeding. It is also known to have significant side effects including bowel ischemia that have significantly limited its use. The long-acting somatostatin analog, octreotide is now the preferred agent over vasopressin owing to its better safety profile. Vasoactive medication may stop bleeding in 75–80% of cases of bleeding due to portal hypertension. The mechanism by which octreotide reduces splanchnic blood flow is not known. Doses for acute GI bleeding are typically in the range of an initial IV bolus of 1 $\mu\text{g}/\text{kg}$ up to 50 μg and then 1–5 $\mu\text{g}/\text{kg}/\text{h}$ as a continuous infusion. Usually the dose is gradually tapered after cessation of bleeding or endoscopic therapy rather than being abruptly stopped and octreotide may be readministered if rebleeding occurs. The role of octreotide is less clear in GI bleeding unrelated to portal hypertension.

Balloon Tamponade

In the child who continues to have uncontrollable variceal bleeding, balloon tamponade may be the only method that can stabilize the patient until a more definitive procedure can be undertaken. The Linton tube is used for small children or if bleeding gastric varices are present, and the Sengstaken-Blakemore tube is used for older children (**Figs 1A and B**). Both are highly effective and can stop esophageal and/or gastric variceal bleeding in up to 90% of patients. Risks associated with balloon tamponade include aspiration, esophageal rupture and ulcers, and airway obstruction.

Endoscopic Management

Among the mucosal lesions amenable to endoscopic therapy are ulcers with active bleeding, oozing from a clot overlying an ulcer, or an ulcer that has a visible vessel at its base. Endoscopic hemostasis of mucosal lesions includes injection, sclerotherapy, variceal banding and thermal methods.

Injection method Epinephrine 1:10,000 in normal saline is injected into and near the periphery of an oozing lesion. Injection therapy may slow or stop active bleeding, but it should be followed by contact thermal coagulation.

Contact thermal methods These procedures achieve hemostasis by local tamponade and coaptive coagulation, which involves fusing the walls of blood vessels up to 2 mm in size. Common contact thermal methods are heater probe, bipolar probes and bipolar circumactive probe (BICAP) cautery. The heater probe allows tamponade with firm direct pressure on a bleeding site, followed by delivery of two to four pulses of 15–30 J to coagulate the lesion. In adults, perforation has been reported in approximately 1% of

patients and rebleeding in 18% of patients after thermal methods. Endoscopic clip placement is a newer technique to capture and compress the tissue surrounding a bleeding vessel.

Sclerotherapy Sclerotherapy for children employs 25-gauge needles to inject volumes of sclerosant based on patient weight. The most common significant complication of injection sclerotherapy is esophageal ulceration leading to stricture formation, which occurs in 15% of all children treated. Details of the procedure have been provided in the previous chapter.

Band ligation Controlled studies in adults have shown that band ligation (**Figs 2A and B**) has a higher efficacy in preventing rebleeding and has fewer complications, lower costs and higher rates of survival. With the development of multiband ligation devices, which allow application of up to six bands per session, pediatric experience with this technique is encouraging. The inability to pass the band ligation apparatus in infants and small children is the only limiting factor.

When a child is bleeding and hemodynamically unstable, both sclerotherapy and band ligation can be technically difficult. In such cases, it is best to monitor the child in an ICU, protect the airway with an endotracheal tube, sedate the patient, and temporarily control the bleeding by passing a Sengstaken-Blakemore tube or Linton tube.

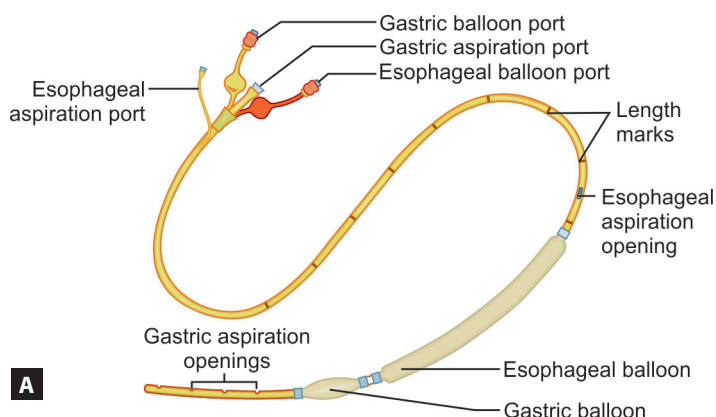
Angiography is employed when an additional therapeutic component is needed, such as placement of a transjugular portosystemic shunt, selective infusion of a vasoactive agent into a bleeding vessel, or embolization of a bleeding vessel with gelfoam or coils.

Surgical Management

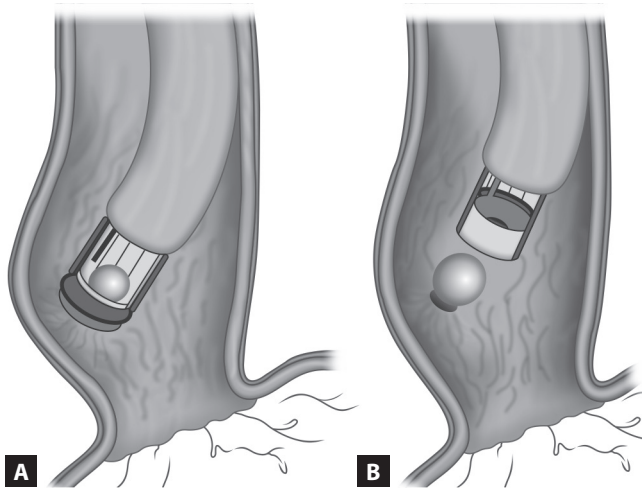
Surgery is indicated in patients with a posterior duodenal ulcer with arterial bleeding, bowel perforation with bleeding, and gastroesophageal varices. Surgical intervention for gastroesophageal varices requires a portosystemic shunt procedure, such as a mesocaval shunt, distal splenorenal shunt, or central portocaval shunt. The esophageal transection and devascularization is potentially life-saving surgery for bleeding esophageal varices which is not amenable to other treatments.

LOWER GASTROINTESTINAL BLEEDING

Lower GI bleeding is defined as bleeding with an origin distal to the ligament of Treitz. The quantity of blood loss may range from stools positive for occult blood to a life-threatening hemorrhage presenting with profound shock. LGI bleeding can present as hematochezia, melena or occult bleeding.



Figures 1A and B (A) Sengstaken-Blakemore tube; (B) Linton tube



Figures 2A and B Band ligation of esophageal varices:
(A) Ligating the bleeder; (B) After the procedure

Epidemiology

In an Indian study done at SGPGIMS, Lucknow, causes of LGI bleeding were colitis (42%), colorectal polyps (41%), enteric fever (5%), solitary rectal ulcer (5%), portal hypertensive colopathy (3%), colonic arteriovenous malformation (1.5%) and internal hemorrhoids (1.5%).

In another study done at a tertiary care emergency department, rectal bleeding represented the chief complaint in 0.3% of all visits. Almost 50% of the children were younger than 1 year old. Allergic colitis was the commonest diagnosis, followed by anorectal fissure, in children younger than 1 year old. Infectious gastroenteritis and anorectal fissure were the commonest diagnoses between 1 year and 5 years and greater than 5 years age, respectively. Causes of LGI bleeding are listed in **Box 2**.

Approach to Lower Gastrointestinal Bleeding

The most important step is the rapid assessment of the degree of volume loss and the initiation of fluid resuscitation if needed. Tachycardia is a very sensitive initial indicator of severe blood loss, whereas slow capillary refill and hypotension are late signs of hypovolemia and shock. Symptoms of hemodynamic instability should prompt urgent placement of large-bore IV catheters and may lead to transferring the patient to the ICU.

History

A detailed family history is important, whether any first-degree relative has history of allergy, inflammatory bowel disease (IBD), familial adenomatous polyposis, hereditary hemorrhagic telangiectasia, Ehlers-Danlos syndrome or bleeding disorders. Any such history is strongly suggestive of the same disease in the presenting child. The occurrence of LGI bleeding soon after weaning and introduction of cow's milk formula in the diet strongly suggests the occurrence of cow's milk protein allergy. History of water source and history of recent travel and eating outside are important in cases of bacterial or viral GI infection, whereas recent travel to an endemic area is suggestive of amebiasis. Recent use of antibiotics is a risk factor for antibiotic-associated diarrhea and pseudomembranous colitis. Exposure to contaminated foods (chicken, eggs, unpasteurized milk) enhances the risk for outbreaks of bacterial GI infection. Age is a very important component of the history for finding the most common causes of LGI bleeding as the causes vary according to the age of the patient.

BOX 2 Causes of lower gastrointestinal bleeding

Presenting with hematochezia and/or melena

- *Intestinal ischemia*: Complicating intussusception, midgut volvulus, incarcerated hernia or mesenteric thrombosis
- *Meckel's diverticulum*
- *Upper GI source*: See hematemesis
- *Vasculitis*: Henoch-Schönlein purpura
- *Sloughed polyp*
- *Intestinal or colonic ulcer*: NSAID gastropathy, Crohn's disease, ulcerative colitis
- *Vascular malformation*

Rectal bleeding with signs of colitis (bloody diarrhea, tenesmus, night-time stooling)

- *Infectious colitis*: *Salmonella*, *Shigella*, *Yersinia enterocolitica*, *Campylobacter jejuni*, *Escherichia coli* O157:H7, *Aeromonas hydrophila*, *Klebsiella oxytoca*, *Clostridium difficile*, *Neisseria gonorrhoeae*, cytomegalovirus, *Entamoeba histolytica*, *Trichuris trichiura*
- *Inflammatory bowel disease*: Ulcerative colitis, Crohn's disease
- *Necrotizing enterocolitis*
- *Eosinophilic proctocolitis*
- *Hemolytic-uremic syndrome*

Rectal bleeding with normal stool pattern

- *Juvenile polyp*
- *Nodular lymphoid hyperplasia*
- *Eosinophilic colitis*
- *Inflammatory bowel disease*
- *Vascular malformation*

Bright red blood coating normal or hard stool

- *Anal fissure*
- *Beta-hemolytic streptococcal cryptitis*
- *Ulcerative proctitis*
- *Rectal prolapse*
- *Solitary rectal ulcer*
- *Internal hemorrhoids*

Occult gastrointestinal blood loss

- *Esophagitis*
- *Reactive gastritis*
- *Acid-peptic disease*
- *Eosinophilic gastroenteritis, colitis*
- *Celiac disease*
- *Inflammatory bowel disease*
- *Polyposis*
- *Meckel's diverticulum*
- *Vascular malformation*

Stool Characteristics

Bleeding which is limited to the outside of the stools or spots of red blood coating the stools or found in the diaper, on the toilet tissue, or in the toilet bowl imply bleeding from an anal or rectal origin.

Table 3 provides an approach to likely diagnosis based on the stool characteristics in a child with LGI bleed. Blood mixed through the stool suggests a colonic source for the bleeding located higher than the rectum, whereas hematochezia mixed with mucus and loose stools suggests colitis. Maroon-colored stools are suggestive of a hemorrhage arising from the distal small bowel. Currant jelly stools are potentially indicative of ischemic bowel lesions, such as those seen in cases of intussusception or midgut volvulus.

Physical Examination

A detailed examination of the anus, perineal area and rectum is essential. Fever suggests the presence of an infectious disease or inflammatory disorder. Failure to thrive may be suggestive of an underlying chronic disease like IBD. Extraintestinal manifestation of IBD, like episcleritis, pyoderma and erythema nodosum should not be missed. Jaundice and signs of chronic liver disease (CLD) should also be seen for evidence of portal hypertension and rectal varices.

Table 3 Etiological diagnosis of lower gastrointestinal bleed as per stool characteristics

Amount	Appearance	Character of stool	Pain	Possibilities
Small	Red	Hard	Yes	Fissure
Small to moderate	Red	Loose	Variable	Allergic, infectious
Small to moderate	Red	Normal coated with blood	No	Polyp
Moderate	Red to tarry	Normal	Yes	Henoch-Schönlein purpura
Moderate	Red to tarry to currant jelly	Normal	Yes	Intussusception
Moderate	Red to tarry	Loose	Yes	Hirschsprung with enterocolitis
Large	Red to tarry	Normal	No	Meckel's diverticulum, angiodysplasia

Common Causes of Lower Gastrointestinal Bleeding

Neonate and Early Infancy

The most important diagnosis to exclude in the neonate with rectal bleeding is necrotizing enterocolitis. The typical presentation is a preterm infant with small amounts of gross blood in the stool, feeding intolerance, and emerging signs of systemic instability. Enterocolitis in a neonate or infant with abdominal distention and impaired defecation may be due to Hirschsprung disease. Colitis in otherwise well-appearing infants is most often due to cow's milk protein allergy. Proctosigmoidoscopy in conjunction with the evaluation of multiple mucosal biopsy specimens may be helpful for diagnosis. Bowel obstruction with ischemic injury (intestinal volvulus, ileocolic intussusceptions) should be suspected in an infant or young child with vomiting, pain, and small amounts of blood in the stool. Doppler ultrasonography can also aid in the diagnosis of midgut volvulus by showing clockwise rotation of the superior mesenteric vein around the superior mesenteric artery (*whirlpool* sign).

Infectious Causes

Infectious enterocolitis can present with bloody stool at any age. Important bacterial pathogens include *Salmonella*, *Shigella*, *Campylobacter*, *Yersinia enterocolitica*, *Clostridium difficile*, and *Escherichia coli* (O157:H7). *Entamoeba histolytica* is the most important parasitic pathogen. CMV can cause enterocolitis in children with primary or secondary immunodeficiency and can present with massive life-threatening hemorrhage. Children with acquired immunodeficiency syndrome (AIDS) can suffer life-threatening GI bleeding from aphthous ulceration in the absence of a detectable infectious cause. Typhlitis, a polymicrobial inflammatory disease in the cecum of severely immunosuppressed patients, can present with massive GI bleeding.

Surgical Causes

Intussusception, Meckel's diverticulum, intestinal/rectal polyps, and other tumors and neoplasms are important causes of LGI bleed.

Intussusception usually occurs in patients 4–10 months of age, with 65% of cases occurring before 1 year and 80% by 2 years of age. The majority of cases occur in the region of the ileocecal valve, and no lead point can be precisely identified. In older children, a lead point, including polyp, Meckel's diverticulum, intestinal duplication, or neoplasm, is more likely to be found. Abdominal pain and vomiting, followed by passage of *currant jelly stool*, representing a mixture of blood, mucoid exudate, and stool, is characteristics of intussusceptions. On examination a palpable sausage-shaped abdominal mass can be palpated. Diagnosis is confirmed by abdominal ultrasonography.

Meckel's diverticulum is usually asymptomatic; however, it can present with LGI bleeding resulting from the ulceration of adjacent ileal mucosa by acid-secreting heterotopic gastric mucosa contained in the diverticulum. LGI bleeding is often brisk and

painless and may present as self-limited recurrent bleeding in an otherwise healthy child or life-threatening acute massive lower hemorrhage. Provided that gastric mucosa is present, the diagnosis of Meckel's diverticulum can be made with an 85–90% sensitivity by a radionuclide technetium 99 m pertechnetate scan showing the presence of heterotopic gastric mucosa in the right lower quadrant of the abdomen (**Fig. 3**). False-positive results of technetium 99 m pertechnetate scintigraphy have been reported in patients with intussusception, hydronephrosis, arteriovenous malformation and IBD. The treatment of choice is surgical excision.

Polyps and tumors Beyond infancy, juvenile polyps are the commonest source of significant rectal bleeding in childhood. Painless, intermittent bleeding is typical. Juvenile polyps are nonneoplastic polyps that contain dilated cystic spaces, infiltrating inflammatory cells, marked vascularity, and areas of eroded epithelium. They predominantly occur in the rectosigmoid but may occur throughout the colon. Children with multiple or recurrent juvenile polyps may have juvenile polyposis coli or juvenile polyposis syndrome, a genetic disorder that has an increased risk of adenomatous degeneration and malignancy. Bleeding from hamartomatous polyps (e.g., Peutz-Jeghers syndrome) is unusual unless accompanied by intussusception and bowel ischemia. Other tumors presenting with rectal bleeding in childhood are rare.

Hemorrhoids: Colonic and Anorectal Varices

Hemorrhoids are unusual in children and if present, portal hypertension should be suspected. One-third of the children with portal hypertension may have hemorrhoids or anorectal varices that are most often totally asymptomatic. Hemorrhoidal bleeding usually presents with bleeding on defecation. Treatment is advised only for symptomatic patients, and injection sclerotherapy is satisfactory for the majority.

Other Causes

Foreign body injury must be considered, including ingested glass, a broken glass rectal thermometer, or other sharp objects. Unexplained bleeding despite extensive evaluation should also raise suspicion of Munchausen's syndrome by proxy.

Investigations

Complete blood count, clotting studies, and routine chemistry are performed unless history taking and physical examination allow the cause of LGI bleeding in the patient to be determined without doubt. The presence of iron deficiency anemia suggests a history of chronic blood loss. Determination of erythrocyte sedimentation rate and/or C-reactive protein is useful when infectious colitis or an inflammatory disorder is being considered. Liver function tests are necessary when liver disease and portal hypertension are suspected to be responsible for LGI bleeding. In cases of invasive bloody diarrhea or suspicion of IBD, stool culture and stool examination for virus, ova and parasites, and *C. difficile* toxin are necessary.

Ultrasonography

Ultrasound examination of the abdomen is helpful in an acute abdominal disorder with obstruction and/or ischemia, or when an abdominal mass is present. It can help in diagnosis of intussusception, malrotation, hepatosplenomegaly, and CLD.

Colonoscopy

Colonoscopy is the preferred diagnostic modality for rectal bleeding. Limited inspection of the rectosigmoid is usually sufficient for infants with allergic colitis and may be adequate to establish an initial diagnosis of infectious, ischemic, or idiopathic colitis in older children. In other cases, complete colonoscopy is preferred to identify focal or multifocal lesions or assess the extent of colonic involvement. Unless ischemia or obstruction is suspected, a suitable bowel preparation should be administered to facilitate optimal visualization and potential intervention.

Bowel preparation is safely achieved in children using standard polyethylene glycol electrolyte. A small-diameter colonoscope (11 mm) can be used in most children beyond 2 years of age. A smaller-diameter gastroscope is required in infants.

Examination of the terminal ileum should be routinely attempted to detect active bleeding from the small bowel or Crohn's disease. Examination of the ileocolic junction is also required to detect the postoperative anastomotic ulceration. Superficial mucosal vascular lesions, such as telangiectasias, hemangioma, or venous malformation, are best visualized by colonoscopy.

Endosonography is comparatively more sensitive than endoscopy for detecting submucosal lesions and may be particularly useful in cases of vascular anomalies.

Radionuclide Scanning

Radionuclide scanning with technetium 99 m pertechnetate is done for suspected cases of Meckel's diverticulum or duplication. In this scan, technetium rapidly binds to the gastric mucosa, has been very useful in making the diagnosis of heterotopic gastric mucosa contained in Meckel's diverticulum or intestinal duplication in children, with an 85–90% sensitivity (**Fig. 3**).

Red blood cell (RBC) scan can also be performed to look for the site of bleeding. In this test, the patient's own red cells are labeled with technetium 99 m pertechnetate and reinjected into the bloodstream. The site of bleeding can be visualized, provided the bleeding rate is 0.5 mL/min or higher.

Angiography

An angiography can be done to evaluate for ongoing LGI bleeding in which esophagoastroduodenoscopy and colonoscopy are negative and bleeding rate is 0.5 mL/min or greater. Angiography can identify a potential bleeding site in 50% of children. Angiography also offers the benefit of selective arterial embolization in tertiary centers with the technical expertise to perform supraselective catheterization. It should be limited to the very few patients with active LGI bleeding and negative EGD and colonoscopy.

Capsule Endoscopy

Obscure GI bleeding, either occult or overt, is the most frequent indication for capsule endoscopy. Capsule endoscopy is a big step forward in the diagnosis of obscure GI bleeding of presumed small bowel origin. Capsule endoscopy is safe and well tolerated and the wireless capsule can make diagnoses beyond the reach of enteroscopes.

Treatment

Medical Therapy

It includes initial resuscitation measures and specific therapy for diseases. Bleeding from allergic colitis of infancy responds

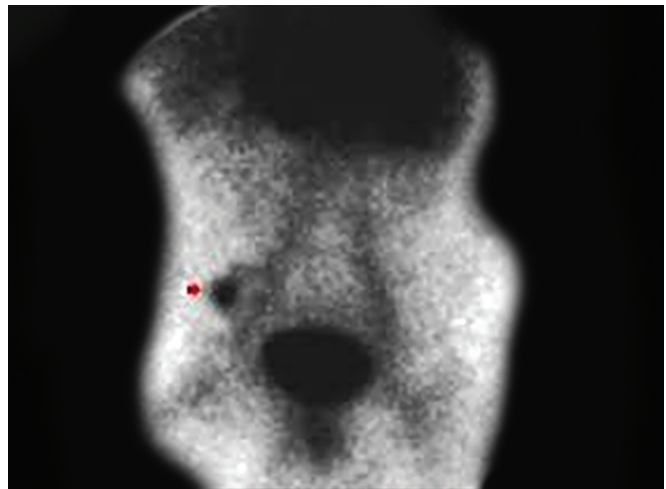


Figure 3 Meckel's scan

promptly to dietary restriction and introduction of hydrolyzed protein formula. Ischemic colitis (necrotizing enterocolitis) is treated supportively with intravenous fluids, IV antibiotics and gut rest. Appropriate antibiotics are used to treat infectious colitis and immunosuppressive and anti-inflammatory agents are used for IBD. Rapidly proliferating hemangiomas have been successfully treated with corticosteroids and with interferon-alpha.

Endoscopic Therapy

Endoscopic therapy is primarily polypectomy for colorectal polyps. Juvenile polyps in children tend to be small to medium diameter (5–15 mm) and are often pedunculated, making resection with minisnares straightforward. Although malignancy is rare, an effort should be made to resect and retrieve all polyps for histopathologic examination to exclude the presence of adenomatous or cancerous epithelium. Hemostatic techniques, such as sclerotherapy, electrocoagulation, laser and elastic band ligation are used in children for vascular colonic anomalies.

Surgery

Surgery is most often indicated for bleeding resulting from nonreducible intussusception or a vascular anomaly. Over the past years, the rates of surgical intervention for intussusceptions have reduced because of the high level of success with pneumatic reduction. Meckel's diverticulum is treated by surgical resection. Patients with vascular anomalies may require excision of focal lesions or surgical resection or exclusion of a larger segment of involved bowel.

OCCULT GASTROINTESTINAL BLOOD LOSS

Occult blood in the stool is detected mostly while evaluating chronic GI symptoms, such as abdominal pain, vomiting, diarrhea, and constipation; unexplained systemic symptoms (weight loss, growth retardation, arthralgia, fever) or unexplained iron deficiency anemia. The most common causes are inflammatory disorders (including esophagitis), acid peptic disease, reactive gastritis, eosinophilic gastroenteritis, celiac disease, Henoch-Schönlein purpura, Crohn's disease, ulcerative colitis, polyps and Meckel's diverticulum. Rare causes of occult bleeding are vascular anomalies, infection and neoplasia. Infectious causes of occult GI blood loss include hookworm, ascariasis, amebic infection, *Strongyloides* infection and tuberculosis.

IN A NUTSHELL

1. Gastrointestinal bleeding in children can arise from the UGI or LGI tract. Hematemesis and melena are characteristic of UGI bleed.
2. Lower GI bleed can present with hematochezia, melena or occult bleed.
3. Most common causes of UGI bleed include stress gastritis, esophagitis and variceal bleeding. LGI bleed is usually because of enterocolitis, polyps, intussusceptions or a Meckel's diverticulum.
4. Upper GI endoscopy and colonoscopy are the preferred diagnostic modalities for diagnosis of bleeding from the UGI and LGI tract, respectively.
5. Treatment should be directed at maintaining the hemodynamic balance, identifying the cause of bleed, and provide specific treatment for both the present episode and also prevention of future episodes.

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Chapter 37.6

Liver Abscess

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Liver abscesses have been increasingly reported in children in recent years, especially from developing countries. The incidence varies from 1 to 79 per 100,000 pediatric admissions. Most of the liver abscesses in children are pyogenic, followed by amebic etiology. Rare causes include tuberculosis, helminthic infections like ascariasis and fungal infection (especially in patients with immunocompromised state).

PATHOGENESIS

Liver abscess can result from seeding of bacteria from portal venous system, biliary system, hepatic arteries or direct extension from surrounding organs like lungs, subdiaphragmatic space or from penetrating injuries (**Fig. 1**). Pyogenic liver abscess (PLA) can also occur due to secondary bacterial infection of amebic abscess or hydatid cyst. Septic emboli secondary to septicemia or thrombophlebitis in portal system (umbilical catheterization, appendicitis, colitis, etc.) get trapped in sinusoids and may become a nidus for abscess formation. Cholangitis is an important etiology for liver abscess, though less common in children than adults. Biliary tract anomalies (choledochal cyst, Caroli disease), choledocolithiasis, biliary ascariasis or post-Kasai portoenterostomy predispose the child to recurrent cholangitis and abscess formation which are almost always multiple.

Immunodeficiency disorders [chronic granulomatous disease (CGD), complement deficiency and hyper-IgE syndrome] may also cause liver abscess as a part of multi-systemic infections. Recurrent abscesses at multiple sites like liver, lung and skin are an important clue to CGD. Malnourished children with poor immune functions and residing in overcrowded, unhygienic conditions in the developing world are also at an increased risk. Invasive intestinal amebiasis is the cause of amebic liver abscess (ALA), although a history of same is not always forthcoming.

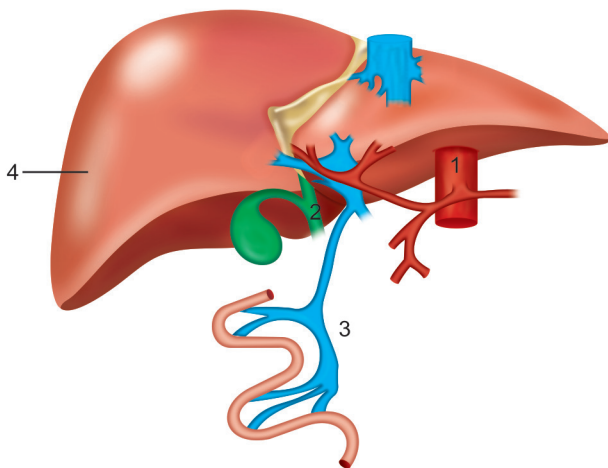


Figure 1 Routes of entry of infection in liver

Keys: 1, Systemic infection through hepatic artery; 2, Infection from biliary tree; 3, Infection from gut through portal vein; 4, Direct trauma/infection from surrounding tissues

PATHOLOGY

The abscess may be single or multiple. The contents are yellow or greenish which may be foul-smelling, particularly if due to anaerobic organisms. Microscopically, acute abscess contains necrosis and polymorphs, and bacteria may or may not be identified on Gram stain. In subacute or chronic abscess, the wall is replaced by granulation and fibrous tissue. Presence of supportive cholangitis or portal pylephlebitis may indicate the source of infection.

Amebic liver abscess is usually single, large and located in posterior portion of right lobe. The abscess contains odorless (unless secondarily infected) reddish-brown pus resembling anchovy sauce. The abscess wall is ragged, and its lining contains three layers: inner most composed of necrosis and occasional ameba, next layer of granulation tissue and fibrosis with few inflammatory cells, and the outer most layer of compressed normal liver tissue.

More than 75% of the liver abscess occur in right lobe of liver and most are solitary; 20–25% are multiple. Right branch of portal vein continues in the direction of main portal vein whereas left branch is more horizontal and this results in relatively more volume and flow of blood from portal system to the right lobe of liver. Thus, infections are more commonly localized to the right lobe of liver.

MICROBIOLOGY

Staphylococcus aureus is the most common etiology of PLA in children, accounting for ~65–85% cases. *Enterococcus faecalis*, *Escherichia coli*, *Klebsiella*, *Acinetobacter baumannii* and *Enterobacter* species are responsible for the remaining cases. Gram-negative organisms are more common in infants. Anaerobic organisms like *Bacteroides fragilis* and *Fusobacterium necrophorum* are also isolated in a small proportion of children. Uncommon organisms include *Salmonella* (as a complication of enteric fever leading to cholangitis), fungi (in immunocompromised states like CGD, leukemia, etc.) and *Mycobacterium tuberculosis*.

Amebic liver abscess is a common extraintestinal manifestation of intestinal amebiasis and constitutes about 20–30% of liver abscess in children reported from developing countries. The diagnosis is made if there is negative pus culture with positive amebic serology. If a patient has both positive amebic serology as well as positive pus culture, it is difficult to know if it is primarily an ALA with secondary bacterial infection or a pyogenic abscess with positive amebic serology due to previous invasive intestinal amebiasis. These cases may be labeled as indeterminate.

In some children, no cause is found and the abscess is labeled as *cryptogenic*. Liver abscess may be polymicrobial in a few patients. The abscess may also be sterile, mostly due to prior antibiotic use or inadequate culture techniques, especially in case of anaerobic organisms.

CLINICAL FEATURES

Pyogenic liver abscess usually presents with fever, right hypochondrium pain and tender hepatomegaly. Other symptoms include fatigue, nausea and vomiting, anorexia and weight loss. Some children may present with pulmonary complications, like consolidation, pleural effusion or empyema. Abscess in sub-diaphragmatic location may cause referred pain to shoulder and cough due to irritation of diaphragm. Some children may present in a very sick state with septicemia and abscesses at multiple sites. **Table 1** shows the common presenting features in series from India and other developing countries.

Most of the patients present insidiously, possibly as a result of inappropriate use of antibiotics, except for a few with fulminant presentation due to sepsis or rupture of abscess into peritoneum

Table 1 Pediatric liver abscess studies

	1986–1997 Pakistan	1990–1996 South India	1991–2000 Kashmir	2000–2008 Lucknow	2010–2012 Delhi
No. of patients	48	18	129	39	53
Age	3 weeks to 14.5 years	3 months to 12 years	18 months to 14 years	7.2 ± 3.9 years	7.3 ± 3.8 years
Male: Female	1.5:1	1.6:1	1.5:1	2:1	0.8:1
Pyogenic	-	100%	54%	64%	92.5%
Amebic	100%	-	4%	28%	7.5%
Ascaridal	-	-	8%	-	-
Others	-	-	34%	8%	-
<i>Symptoms</i>					
Fever	100%	100%	100%	97%	96%
Abdominal pain	81%	77%	90%	95%	92%
Hepatomegaly	100%	83%	86%	97%	NA
<i>Complications</i>					
Pulmonary	2%	-	-	28%	21%
Rupture	2%	-	9%	31%	15%
UGI bleed	-	-	-	10%	-
Jaundice	4%	-	-	5%	-
<i>USG</i>					
Single	92% (75%/17%)	78% (67%/11%)	NA	67% (70%/20%)	77% (92%/8%)
(Right/Left lobe)	8%	22%		33%	23%
Multiple					
<i>Organisms</i>					
<i>Staphylococcus</i>	NA	64%	Most common	58%	Most common
Gram negative*		36%		42%	
<i>Treatment</i>					
Antibiotics	42%	55%	38%	20%	28%
PNA [†] /PCD [‡]	58%	28%	19%	62%	51%
Surgical drainage	0	17%	43%	18%	21%
Mortality	0%	11.1%	4.7%	2.5%	3.7%

*Gram negative bacteria included *Acinetobacter baumannii*, *Escherichia coli*, *Enterococcus faecalis*, *Klebsiella pneumoniae*, *Salmonella typhi*.

[†]PNA, percutaneous needle aspiration.

[‡]PCD, percutaneous drainage; NA, not available.

or pleural space. Most of the patients with amebic abscess present subacutely with low-grade fever, dull aching right upper abdominal pain, weight loss, fatigue and anemia. Clinical features usually do not help to differentiate ALA from PLA. ALA is reported to occur in ~1–7% of invasive amebiasis. However, less than 50% patients give history of diarrhea in the recent past and ~10% patients may concomitantly have dysentery with ALA. Jaundice is uncommon in liver abscess, except when it occurs due to biliary obstruction and cholangitis. Splenomegaly may be seen in few cases. Upper gastrointestinal bleeding (UGIB) may occur, mostly due to erosions/ulcer secondary to nonsteroidal anti-inflammatory drug intake or stress. Presence of UGIB with jaundice suggests hemobilia. In contrast to the developed world, where immunodeficiency states and intra-abdominal sepsis are often seen in patients with liver abscess, no predisposing factor is usually seen in patients in the developing world. Neonates with liver abscess present with non-specific symptoms and a high index of suspicion is required, particularly in high-risk groups like premature babies and those with necrotizing enterocolitis or umbilical catheterization.

INVESTIGATIONS

The aim of investigations is to confirm the diagnosis, determine the etiology, detect presence of complications and plan management.

- **Hematology and biochemistry:** Leukocytosis, anemia and raised ESR are common. Liver function tests show elevated alkaline phosphatase and hypoalbuminemia with mild elevation of transaminases in some patients. Low platelet

count with deranged prothrombin time suggests disseminated intravascular coagulation (DIC) in patients with coexistent septicemia.

- **Chest X-ray:** Elevation of right dome of diaphragm and collapse of right basal segments of lung with pleural effusion may be present. Increase cardiothoracic ratio suggests presence of pericardial effusion.
- **Blood culture** should always be sent in all cases with liver abscess prior to starting antibiotics. Pus aspirated from the liver abscess or abscess at other sites should be sent for Gram stain and culture sensitivity (aerobic and anaerobic). Trophozoites of ameba are usually not detected in aspirates from amebic abscess, as they are located in the abscess wall.
- **Amebic serology:** ELISA or hemagglutinin tests are useful investigations with sensitivity and specificity of ~95%. In endemic areas, a positive serology may not be helpful in diagnosis, but a negative serology favors pyogenic over ALA.
- **Ultrasonography:** It is the imaging of choice as it is cheap, safe, easily available and has a good diagnostic accuracy. Abscesses are round or oval, with thick walls and irregular margin. Early suppuration appears as hypoechoic solid mass while completely liquefied abscess appears as a cystic lesion, which may be anechoic. Multiple septae and internal debris may also be seen. Ultrasonography can detect abscess of size as small as 1.5 cm with a sensitivity of 90%. In addition to liver abscess, other intra-abdominal collections, ascites, biliary obstruction and pleural effusion can also be assessed. Impending rupture

is suggested when the liver rim around the abscess is less than 1 cm. The differential diagnoses of liver abscess include hydatid cyst, hematoma and simple cyst with hemorrhage or infection. Rarely, neoplastic lesions like lymphoma and metastases from neuroblastoma or Wilms tumor may simulate abscess.

- **Other imaging modalities:** Contrast enhanced CT scan is required in some cases. It helps in providing information about the accurate location, presence of air within abscess, relation to surrounding structures, and features of rupture and other complications. In noncontrast CT, abscess appears as a hypodense lesion which shows rim enhancement on contrast injection. In large abscesses, multiple septations may give a *honeycomb* appearance (**Fig. 2**).

MRI is more sensitive to detect small abscess and it is required in select cases, e.g., biliary disease. Abscesses are hypointense on T1 and hyperintense on T2 weighted images, and they show enhancement on gadolinium contrast.

MANAGEMENT

The main pillars of management are antibiotics, supportive therapy, and drainage (percutaneous or surgical) (**Flow chart 1**). *Supportive therapy* consists of antipyretics, analgesics and intravenous hydration. Management of complications like empyema, correction of anemia and nutritional support in malnourished children is very important.

Antibiotics

Correct choice and duration of antibiotic is essential. A combination of cloxacillin or vancomycin, third generation cephalosporins, and metronidazole is a good first choice in children. Later, the antibiotics can be changed as per culture sensitivity and clinical response. Injectable antibiotics are preferred for the initial 2 weeks or until the patient is afebrile. Thereafter, oral antibiotics are given for a total duration of 4–6 weeks. A longer duration of antibiotics with antifungals is required for CGD patients with liver abscess. Most of the ALA respond to antiamebic therapy. Metronidazole is the drug of choice (35–50

mg/kg/day in 3 divided doses for 10 days, IV or oral). Tinidazole (50 mg/kg/day for 5 days) followed by paramomycin (25–35 mg/kg/day in 3 divided doses for 7–10 days) or diloxanide furoate (500 ng TDS \times 5 days) may also be used.

Drainage

Nearly 40–80% hospitalized children with liver abscess require drainage (**Table 1**). There are two main modalities of drainage: percutaneous (needle aspiration or catheter drainage) and open surgical drainage. Percutaneous drainage is preferred as it is less invasive, cheap and gives good results. The indications for drainage largely include nonresponse to antibiotics (persistence of fever or features of persistent sepsis after 48–72 hours of antibiotics) or presence of complications (**Flow chart 1**).

Percutaneous Drainage

Percutaneous catheter drainage (PCD) is more efficacious than percutaneous needle aspiration (PNA). *Needle aspiration* may be tried in solitary, small, unilocular abscess. Though it provides pus for culture sensitivity, multiple sessions may be needed, and there is a risk of peritoneal contamination and inadequate drainage. *Catheter drainage* is preferred in patients with large abscess (> 6 cm), abscess with impending rupture or localized rupture and also in critically ill patients as a temporary measure before surgery. Catheter is removed when there is reduction of size of abscess cavity and drain output is less than 10 mL for three consecutive days. The average duration of PCD is about 7–14 days, and it is successful in about 90% cases. Complications include iatrogenic infection, hemorrhage (into peritoneum or hemobilia) and bile leak.

Open Surgical Drainage

It is the modality of choice in patients with ruptured abscess with peritonitis, multiple large abscesses, multiloculated abscess, thick pus not drainable by catheter, failed PCD and patients requiring surgery for other coexistent abdominal conditions. Intraoperative approach allows drainage of multiple abscesses and intraoperative USG helps to identify deep-seated abscesses. In patients not responding to antibiotics and drainage, other causes like tubercular abscess, fungal abscess or infected hydatid cyst should be considered.

COMPLICATIONS AND OUTCOME

Rupture into surrounding organs (pleural space leading to empyema and hepatopulmonary fistulas, subdiaphragmatic space and peritoneum leading to peritonitis, pericardium causing pericardial effusion and tamponade) is the most common complication. Septic shock, hemobilia, portal vein or hepatic vein thrombosis are the other complications. Large and multiple abscesses, sepsis, hypoalbuminemia, jaundice, encephalopathy and liver failure are poor prognostic indicators. Mortality in liver abscess ranges from 0% to 11%, with a decrease over the last two decades due to advances in imaging and interventions (**Table 1**).

PREVENTION

Prompt treatment of infections (gastrointestinal, biliary and others) with appropriate antibiotics can prevent development of PLA. Correction of malnutrition, anemia and provision of safe water and food to children in developing world will also go a long way in preventing infectious diseases including liver abscess.

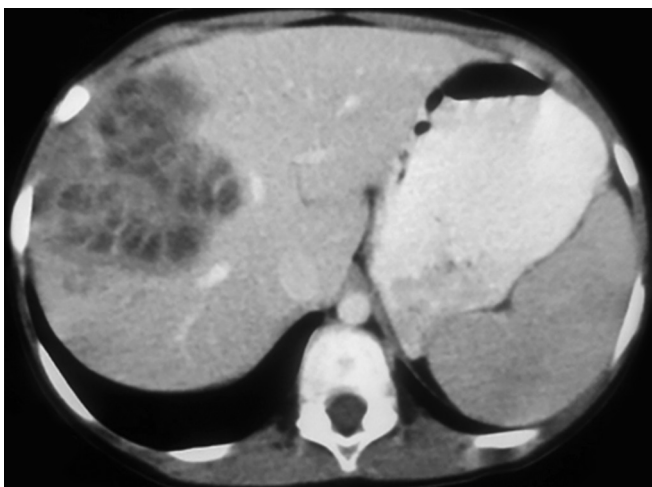
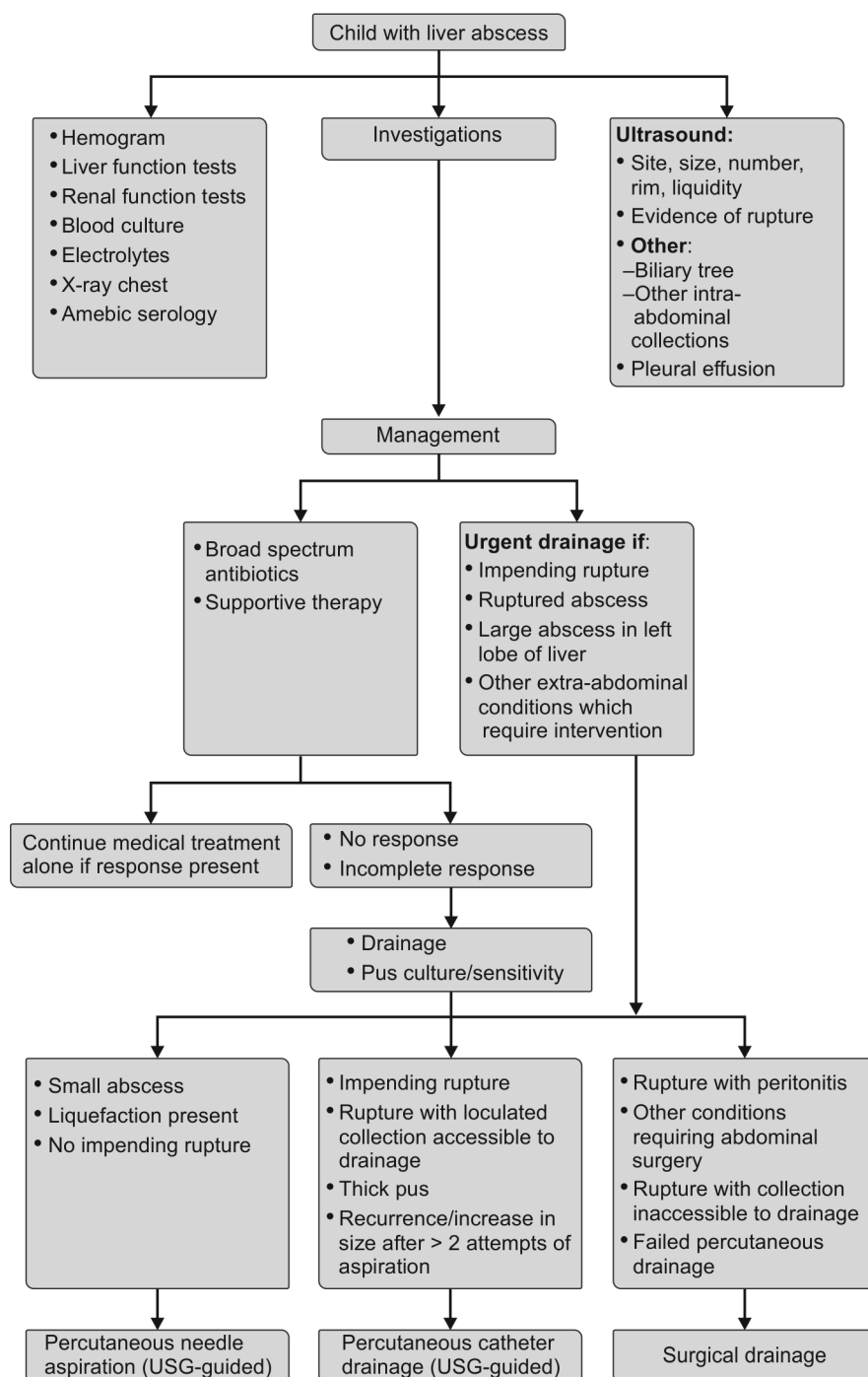


Figure 2 CT scan showing a multiloculated liver abscess (*honeycomb*) with impending rupture

Flow chart 1 Approach to management of liver abscess

IN A NUTSHELL

1. Most liver abscesses are pyogenic, less commonly amebic, and rarely tubercular or fungal.
2. Predisposing factors include malnutrition, intra-abdominal infections, immune deficiency disorders, particularly CGD and biliary anomalies.
3. Most of the abscesses are single and occur in the right lobe. Fever, right hypochondrial pain and tender hepatomegaly are predominant presenting features.
4. *Staphylococcus* is the most common organism in pyogenic abscesses. Gram-negative organisms are commoner in infants. *Entamoeba histolytica* causes ALA.
5. Ultrasonography is the first imaging modality for diagnosis. CECT scan is required in complications like rupture, or where USG is not diagnostic.
6. Complications include rupture into surrounding organs (peritoneum, subdiaphragmatic space, pleural cavity), jaundice, hemobilia and dissemination of infection with septic shock.
7. Antibiotics and drainage is the mainstay of treatment. A combination of cloxacillin/vancomycin with ceftriaxone and metronidazole is given first and later modified as per response and culture sensitivity of isolated organism. Recommended duration of antibiotics for pyogenic abscess is 4–6 weeks.
8. Ultrasound-guided percutaneous drainage (needle aspiration or catheter drainage) is preferred over open surgical drainage. Drainage is indicated in patients not responding to antibiotics in 48–72 hours, impending rupture, or rupture.

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Chapter 37.7

Acute Hepatitis

Barath Jagadisan

Acute hepatitis is a nonspecific term that refers to an acute inflammation of the liver resulting from a wide range of etiologies. Even though the presentation may be acute, it does not always result from an acute disease process. Many of the etiologies may have a long-standing silent disease process preceding the acute presentation. The clinical presentation can be overlapping and therefore, finding the etiology of acute hepatitis can be a diagnostic challenge. Depending on the etiology, acute hepatitis may show a self-limiting course; or recovery in response to treatment or withdrawal of offending agent. It may also result in a fulminant course leading to an acute liver failure (ALF).

DEFINITION

The syndrome of *acute hepatitis* is usually diagnosed in the presence of elevated serum transaminases. The cut-off for diagnosis is usually variable ranging from five to ten times elevation to the upper limit of normal. Alkaline phosphatase (ALP) elevation is seen in all cases of acute hepatitis but is usually less than three times of upper limit of normal. The ALP elevation is proportionately less for the degree of jaundice if present. Visible jaundice or bilirubin elevation is not a must for the diagnosis of acute hepatitis. A pathological diagnosis of acute hepatitis on liver biopsy specimen is made if it reveals hepatocellular necrosis which may range from patchy necrosis to zonal necrosis and massive necrosis associated along with evidence of inflammation. The histopathology looks similar across most of the conditions and, therefore, is often not useful in etiological diagnosis.

CLINICAL FEATURES

Acute hepatitis resulting from most etiology has similar clinical features. The characteristic clinical features of acute hepatitis include nausea, vomiting, right hypochondrial pain and jaundice. The prodromal phase of nonspecific symptoms, including myalgia and anorexia, is characteristic of viral hepatitis, but may also be seen in other conditions. Severe cases manifest with encephalopathy, coagulopathy, sometimes ascites and other features of ALF. Further clinical evaluation may point toward specific etiology.

The disorders that may present with acute hepatitis are listed in **Table 1**. Nonhepatotoxic conditions, like acute cholangitis and large tumor emboli of the liver may also have an *acute hepatitis*-like presentation. Common causes are discussed below.

Infections with Hepatotropic Viruses

Hepatotropic viruses are the most common causes of acute hepatitis worldwide. Hepatitis A virus (HAV) and hepatitis E virus (HEV) are transmitted by feco-oral route, while Hepatitis B virus (HBV) and Hepatitis C virus (HCV) are parenterally transmitted. The parenterally transmitted viruses also cause chronic hepatitis and cirrhosis.

Hepatitis A virus is the most common cause of acute viral hepatitis in India. More than 80% of children over 10 years of age are seropositive for HAV. The infection may be asymptomatic or present with anicteric hepatitis in children of age less than 2 years. Children older than 5 year are more likely to present with acute hepatitis. Up to 50% of children between the age of 6–14 years present with jaundice as opposed to only 10% of children below 6 years of age. The presence of a phase of prodrome preceding

Table 1 Etiology of acute hepatitis in children and adolescents

Viral etiologies
• Hepatotropic viruses:
– Hepatitis A virus
– Hepatitis E virus
– Hepatitis B virus (acute infection and also reactivation of chronic infection)
– Hepatitis C virus (not common)
– Hepatitis D virus in patients with hepatitis B infection
• Nonhepatotropic viruses:
– Cytomegalovirus
– Epstein-Barr virus
– Adenovirus
– Enterovirus
– Herpes simplex virus
– Dengue virus
– Coxsackievirus
– Paramyxovirus
– Rubella
– Varicella-zoster
– Arbovirus
– Parvovirus B ₁₉
Nonviral infections
• Leptospirosis
• Enteric fever
• Tuberculosis
• Histoplasmosis
Drug-induced liver disease
Autoimmune liver disease
Wilson disease
Ischemic hepatitis
Acute Budd-Chiari syndrome
Systemic diseases , e.g., systemic lupus erythematosus, macrophage activation syndrome associated with juvenile idiopathic arthritis, hemophagocytic lymphohistiocytosis presenting with liver failure
Reye's syndrome
In pregnant adolescents
• Acute fatty liver of pregnancy
• HELLP syndrome (hemolysis, elevated liver enzymes, low platelets)

the jaundice, which is characterized by anorexia and nonspecific symptoms, is very characteristic of viral hepatitis. The case fatality rate, resulting from acute liver failure (ALF) in HAV infection, is less than 1% in children. Relapsing hepatitis with intervening improvement of hepatitis is unique to HAV infection. There may also be a phase of cholestatic hepatitis where the transaminases start falling and the bilirubin elevation with predominant ALP elevation are accompanied by pruritus. The diagnosis is usually confirmed by demonstrating IgM anti-HAV antibodies.

In some areas of India, HEV infection is endemic and causes acute hepatitis which is indistinguishable from that caused by HEV. The diagnosis may be established by demonstrating IgM anti-HEV antibody. ALF is less common with HEV than HAV infection.

Hepatitis B virus (HBV) infection is more often seen in children as a result of vertically transmitted chronic infection which remains in an immunotolerant phase in the initial few years of life. Horizontally transmitted HBV infection may also present as acute hepatitis and in such cases the infection frequently gets cleared. Otherwise it persists as a chronic infection. In the background of chronic HBV infection, an acute on chronic hepatitis may occur due to immune activation attempting at clearance of the virus, which may or may not result in seroconversion. Similarly, reactivation

of HBV virus years after seroconversion may also lead to an acute hepatitis even though this phenomenon is more likely to be seen in an older adult. The diagnosis is made by looking for hepatitis B surface antigen (HBsAg) and IgM anti-HBc antibody. HBsAg may be absent during seroconversion in acute HBV infection or rarely in the setting of chronic HBV infection when HBsAg is being lost and anti-HBs antibody appears. IgM anti-HBc antibody, therefore, should be sent in all cases. It diagnoses acute HBV infection even in the absence of HBsAg in acute infection. It should be remembered that demonstration of IgM anti-HBc antibody is not specific for acute HBV infection as it is also seen in exacerbation of hepatitis in chronic HBV infection, even though the titers may be comparatively low. In a given case, unless there is previous documentation of a chronic infection or there is clinical or histopathological evidence of chronicity, confident differentiation between an acute HBV infection and acute exacerbation of a chronic hepatitis based on the titers of IgM anti-HBc antibody alone can be difficult.

Hepatitis C virus infection rarely presents with an acute hepatitis like picture.

Infections with Nonhepatotropic Viruses

Epstein-Barr virus infection presents with features of infectious mononucleosis along with hepatitis. Cytomegalovirus infection presents with mononucleosis like syndrome and acute hepatitis is a part of this systemic disorder. Herpes simplex virus (HSV) infection and enterovirus infection are important causes of acute hepatitis and liver failure in the neonatal period. The presence of vesicles and definite demonstration of HSV in the mother are not essential in the diagnosis of HSV infection in a newborn. Since a delay in diagnosis increases mortality, all children with neonatal liver failure are treated with acyclovir directed against HSV. In India, dengue has been known to present with features of acute hepatitis.

Nonviral Infections

Leptospirosis is a frequent cause of acute febrile hepatitis in India. The illness is biphasic and may be anicteric. The second phase may be characterized by aseptic meningitis, myalgia, nausea and vomiting. In the severe form of the disease, leptospirosis is a febrile icteric illness with high bilirubin in the presence of a moderate transaminase elevation. This dissociation is because of the absence of hepatic necrosis in leptospirosis. Acute kidney injury resulting from acute tubular necrosis is characteristic of the illness. Hemorrhagic manifestations are accompanied by features of capillary leak. The febrile illness, presence of similar infections in the community in an endemic area or during an epidemic and the dissociation between the bilirubin and the enzyme are useful clues in diagnosis.

Enteric fever is a common infection in India and a common differential diagnosis of acute viral hepatitis, the only major differentiating feature being the presence of fever. The jaundice in enteric hepatitis is usually mild initially. The acute febrile hepatitis of enteric fever may even manifest as ALF. The ratio of alanine aminotransferase (ALT) to lactate dehydrogenase (LDH) (in multiples of the upper limit of normal) that is less than 4 is often suggestive of enteric hepatitis. Enteric fever may also manifest as cholecystitis or liver abscess.

In the Indian context, it is to be remembered that simultaneous infections are not uncommon, for example, hepatitis A infection occurring along with enteric fever. Other common infections like scrub typhus occurring in endemic areas are also known to cause acute hepatitis.

Malaria, a common endemic infection, presents with conjugated jaundice in severe cases due to hepatopathy. This malarial hepatopathy is a febrile illness in which the transaminase

levels are usually low but high levels have also been documented. Invariably, acute inflammation is never seen in malarial hepatopathy and hence does not qualify as *hepatitis* in the strict sense of the term.

Autoimmune Liver Disease

Autoimmune liver disease (AILD) is a chronic disease characterized by autoantibodies against antigens in the liver leading to progressive liver damage. This may or may not be associated with autoimmune diseases affecting other organs. In up to 40% of the cases, the presentation may be in the form of an acute hepatitis. AILD is more often seen in adolescent girls but it may be seen even in young children including infancy. The type 1 AILD is characterized by antibodies to smooth muscle antigen (anti SMA) and antinuclear antibodies (ANA) while the type 2 has antibodies to liver-kidney microsomes type 1 (anti-LKM 1). Over two-thirds of AILD in children is type 1. Both types can present with acute hepatitis but a presentation with ALF is more often seen in type 2. The diagnosis of AILD in this situation is usually suspected after infectious, drug, toxic and metabolic disorders are ruled out. Investigating for IgG elevation and anti-SMA and ANA at 1:20 dilution and anti-LKM 1 at 1:10 dilution are part of work-up but elevation of IgG or seropositivity for the autoantibodies are not essential for a diagnosis of AILD. Even though the classical histopathological feature of AILD is described as an interface hepatitis and plasma cell infiltration, these are always not found. The absence of plasma cell infiltrate does not rule out AILD. Centrilobular necrosis as seen in acute viral hepatitis and toxic hepatitis may be seen with a mononuclear infiltrate. AILD may manifest as steatosis or steatohepatitis. Close attention to details might reveal associated autoimmune disease in 20% cases. Early diagnosis of AILD hinges on carefully excluding other etiology.

Wilson Disease

Wilson disease, one of the most common causes of chronic liver disease in children, may present with manifestations suggesting an acute hepatitis. Often such presentation can be fulminant, resulting in liver failure. In the setting of an ALF, diagnosis of Wilson disease can be a challenge. Kayser-Fleischer ring is not present in most children with hepatic presentation in the first decade. The demonstration of a low ceruloplasmin in ALF may not be indicative of Wilson disease as it may very well be the result of poor hepatic synthetic function. Elevated 24-hour urine copper may also be ascribed to the extensive liver necrosis in ALF. A family history may not be present in every case. Associated neurological manifestations or preceding deterioration in school performance or handwriting, if present, might give a clue. Up to one-fourth of these patients may have an associated Coomb's negative hemolytic anemia or a hemolytic episode in the past. The aspartate aminotransferase (AST) is raised more than the ALT, indicating the mitochondrial damage that is characteristic of Wilson disease. Also the ALP is disproportionately low for the bilirubin elevation. A ratio of ALP in IU/L to serum bilirubin level in mg/dL that is less than 2 is indicative of possible Wilson disease. More often the diagnosis is made from a combination of findings that include hemolysis and the above-mentioned enzyme ratios. Children with acute fulminant form of Wilson disease may also have renal failure because of the pigmentary acute tubular necrosis caused by hemolysis. Presentation with ALF, especially with renal failure, almost always requires liver transplantation for survival. For lesser degrees of decompensation, the new Wilson index is used to predict survival (**Table 2**). Children with a score of more than 11 do not survive without transplantation. This score needs to be validated further with larger studies.

Table 2 Prognostication in Wilson disease—the new Wilson index

Score	Serum bilirubin ($\mu\text{mol/L}$)	International normalized ratio	Serum aspartate transaminase (IU/L)	Total leukocyte count ($10^9/\text{L}$)	Albumin (mg/dL)
0	0–100	0–1.29	0–100	0–6.7	> 4.5
1	101–150	1.3–1.6	101–150	6.8–8.3	3.4–4.4
2	151–200	1.7–1.9	151–300	8.4–10.3	2.5–3.3
3	201–300	2.0–2.4	301–400	10.4–15.3	2.1–2.4
4	> 300	> 2.4	> 400	> 15.3	< 2

Note: Score more than or equal to 11 indicates poor prognosis and mortality.

Drug-induced Liver Disease

Drugs are known to produce a varied spectrum of hepatic injury. Acute hepatitis is most common manifestation of drug-induced liver disease (DILI). Drug-induced liver injury is classified based on the histopathological features in liver biopsy. In acute hepatitis, it manifests as inflammatory infiltration along with zonal, bridging, patchy or panlobular necrosis (depending on the drug and the severity of the injury). Biochemically, predominant hepatocellular damage is characterized by an ALT level greater than two times the upper limit of normal or the ALT-to-ALP ratio is more than or equal to 5. There may also be a picture of overlap between hepatitis and cholestasis.

Based on the probable mechanistic model of causation and the clinical and laboratory features, two different types of acute hepatitis are known: (1) *immunoallergic type* and (2) mediated through *metabolic idiosyncrasies*. The former is not related to the dose of the offending drug. It starts manifesting anytime from 2 to 10 weeks after starting the drug and is not usually affected by other coadministered drugs. The illness is usually preceded or associated with fever and extrahepatic manifestations like rash and lymphadenopathy. From one-third to two-thirds of these patients have eosinophilia on peripheral smear and also demonstrated in tissues. Autoantibodies may be demonstrable. The disease subsides rapidly with the withdrawal of the drugs and reappears rapidly in a few days of reintroduction. Drugs, like phenytoin, sulfonamides and nitrofurantoin are known to present with immunoallergic hepatitis.

In contrast, *metabolic idiosyncrasies* are known to be underlying mechanism in acute hepatitis caused due to isoniazid and pyrazinamide. The onset of liver injury ranges from 2 weeks to 6 months and in some cases up to 1 year. There may not be a dose relation to the injury as the hepatitis is a result of metabolic idiosyncrasies. A few drugs are known to have a partial relation to the dose. Coadministered drugs may affect metabolic pathways and augment liver injury. Unlike in the previous type, fever and extrahepatic systemic manifestations are not usually seen. Eosinophilia and autoantibodies are less common. The recovery may not be dramatic with drug withdrawal and the children may continue to worsen or recover slowly. Rechallenge after recovery may result in recurrence of manifestations but unlike in the immunoallergic type, one-third of these children may tolerate the drug with no symptoms and if at all with only mild transaminase elevation.

Acetaminophen toxicity is a dose dependent liver injury that may have very high transaminase levels but has predominantly zonal or massive necrosis in the liver without much inflammation to qualify as hepatitis.

Phenytoin Hepatotoxicity: A Prototype for Immunoallergic Reactions

Phenytoin, a commonly used anticonvulsant, is known to cause a wide range of hepatic manifestations. Yet the most common form is acute hepatitis, which can be life-threatening when associated with liver failure. The hepatitis due to phenytoin may be mistaken for

mononucleosis-like syndrome caused by viruses as it presents with systemic manifestations of fever, lymphadenopathy, leukocytosis, and lymphocytosis. Eosinophilia is prominent. Skin reactions may range from morbilliform lesions to Steven-Johnson syndrome and toxic epidermal necrolysis. The hepatic involvement may be restricted to transaminitis and mild jaundice or may go on to hepatic failure with ascites and encephalopathy. The histopathology may be characterized by inflammation, patchy necrosis or more extensive hepatocellular loss. Prompt withdrawal of the drug is important. Despite the anecdotal nature of the evidence, steroids are often used in these cases. The possible mechanism is a deficiency of an epoxide hydrolase enzyme that is involved in the detoxification of the arene oxide metabolite of phenytoin, thereby resulting in haptens that initiate an immunological injury. There is also an evidence against this hypothesis, thus questioning the exact mechanism. There is also a suspicion that coadministration of phenobarbitone may increase the severity of phenytoin induced hepatotoxicity.

Isoniazid Hepatotoxicity: A Prototype for Hepatitis Due to Metabolic Idiosyncrasies

Isoniazid is a common cause of acute hepatitis in India. Patients on both therapeutic and prophylactic isoniazid may develop acute hepatitis. The frequency is higher with simultaneous use of rifampicin and pyrazinamide. Patients with severe types of tuberculosis, like meningitis and malnourished children, tend to develop acute hepatitis more often. The simultaneous use of phenobarbitone is a potential setting for acute hepatitis. This may be due to cytochrome p450 stimulation by phenobarbitone. It is believed that rapid acetylators who synthesize the acetyl isoniazid intermediate faster have higher rates of liver injury. There may be partial dose relation to the hepatotoxicity even though some studies do not show higher frequency of hepatitis with higher doses.

Usually 10% of the patients on isoniazid are known to develop transient elevation in transaminases. Up to one-third of patients have been documented to have transaminitis in other studies. Patients with elevation of transaminase levels above five times the baseline values, especially with bilirubin elevation, warrant withdrawal of the drug. Elevation over ten times of the baseline is known to develop severe symptoms. Symptoms include nonspecific features, such as anorexia, nausea and vomiting. Systemic features, such as fever, lymphadenopathy, rashes and eosinophilia are not seen. The patient may develop jaundice and features of liver failure such as encephalopathy and coagulopathy. Liver failure indicates poor prognosis and may result in liver transplantation. Patients, in whom the drug is stopped early before the onset of failure, tend to improve with drug withdrawal.

The histopathology in half of these patients shows a picture indistinguishable from acute hepatitis with patchy necrosis and inflammation along with hydropic changes in the rest of the cells. Massive hepatocellular necrosis is seen in severe cases.

Rechallenge with the drugs has been shown to produce an accelerated recurrence of symptoms, but Indian studies show that, with gradual reintroduction of the drug, majority of the patients can be restarted on the drug.

Serial monitoring of enzymes is advocated after starting isoniazid to detect hepatitis early but this does not prevent all cases of hepatitis. The monitoring protocol can be quite variable. Attention to symptoms and detecting the early nonspecific features can be very useful.

Ischemic Hepatitis

Ischemic hepatitis is more commonly seen in a hospital setting in a child who has experienced a hypotensive episode as a result of either septic shock or hemorrhage or congestive cardiac failure with or without an underlying cardiac condition. Documentation of hypotension may not be there in all cases. The child presents with high levels of serum transaminases (in thousands). Transient elevation of prothrombin time may also be seen. The rise in bilirubin is seen after 1 or 2 days. The transaminases normalize rapidly in 7–10 days. The survival of the patient depends on the underlying precipitating condition rather than on the liver injury itself. The importance lies in recognizing the entity and avoiding confusion with either viral, autoimmune, toxic, or drug induced liver injury. The associated LDH elevation with an ALT to LDH ratio less than 1.5 might help in differentiating from viral hepatitis. Even though liver biopsy is not warranted and never done for the condition itself, biopsy might show necrosis, especially centrilobular. This might mimic the necrosis in viral hepatitis, except for the fact that inflammation is characteristically absent. Thus, histopathologically this entity does not behave as *hepatitis*.

TREATMENT

Close monitoring of liver function tests for any worsening of prothrombin time and clinical features suggestive of liver failure is an essential aspect of early supportive management. Specific management may vary depending on the etiology. Early withdrawal of the offending drug, early immunosuppression in autoimmune hepatitis and appropriate antibiotics in case of leptospirosis and enteric fever are a few examples. D-Penicillamine in case of Wilson disease may not be effective in cases presenting as ALF and renal failure and early transplantation is necessary. No disease-specific treatment is applicable for HAV or HEV-induced acute viral hepatitis or ischemic hepatitis.

MORE ON THIS TOPIC

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IN A NUTSHELL

1. Acute hepatitis is a nonspecific term that refers to an acute inflammation of the liver resulting from a wide range of etiologies.
2. It is characterized by elevated transaminases with or without jaundice along with ALP elevation that is proportionately less in comparison to the degree of jaundice.
3. Liver biopsy in acute hepatitis may show hepatocellular necrosis which may range from patchy necrosis to zonal necrosis and massive necrosis associated along with evidence of inflammation.
4. It does not always result from an acute disease process.
5. Acute viral hepatitis caused by HAV is the most common cause of disease in children in India.
6. Enteric fever and leptospirosis are important causes of acute febrile hepatitis.
7. Drug induced hepatitis is not uncommon and a careful history and early withdrawal can be lifesaving.
8. Presence of hemolysis, the ratio of AST to ALT and ratio of ALP to bilirubin can be useful pointers toward a diagnosis of Wilson disease when it presents with ALF.
9. The absence of autoantibodies does not rule out the possibility of autoimmune hepatitis as a cause of acute hepatitis.
10. Close monitoring of INR is essential in managing a case of acute hepatitis.

Chapter 37.8

Chronic Liver Disease

Seema Alam, Rajeev Khanna

Chronic liver disease (CLD) refers to a spectrum of liver diseases including a wide range of disorders which may be genetic or acquired. These disorders may be infective, metabolic, storage, vascular, structural and autoimmune. The definition for CLD, which includes the symptom duration of more than 6 months or 26 weeks, may not apply to infants where many inborn errors of metabolism cause CLD yet are apparent for less than 6 months. Since most acute liver diseases settle down within 12 weeks, any prolongation should raise suspicion of potential CLD. CLD is defined based on evidences seen clinically, biochemically, radiologically and histopathologically (**Table 1**).

The clinical spectrum of CLD may vary from asymptomatic presentation, organomegaly, jaundice, to end-stage liver disease. Recognizing CLD early is important in children as some of these disorders are reversible with early intervention. Compensated CLD is likely to be asymptomatic and go unrecognized. On decompensation, CLD becomes symptomatic with jaundice, encephalopathy or ascites. If the acute decompensation has rapidly developed within 4 weeks in the foreground of pre-existent CLD, then this syndrome is called *acute on chronic liver failure* (ACLF) (**Box 1**). Causes of acute decompensation could be acute viral hepatitis, drug or exacerbation of the underlying cause of CLD.

BOX 1 Definition of acute on chronic liver failure

Acute on chronic liver failure (ACLF) is defined as acute hepatic insult manifesting as jaundice and coagulopathy (Bilirubin > 5 mg/dL, INR > 1.5) complicated within 4 weeks by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease.

Abbreviation: INR, international normalized ratio.

CLASSIFICATION

Parenchymal CLD Presence of jaundice with or without ascites, coagulopathy and hepatic encephalopathy (HE) would suggest a parenchymal liver disease. Parenchymal CLD cases can be broadly categorized into infective, metabolic (including storage), immunologic and vascular etiologies (**Table 2**).

Cholestatic CLD Presence of jaundice, pruritus, and clay stools suggest a biliary disease causing cholestatic CLD. Causes of cholestasis in children are depicted in **Table 2**.

EPIDEMIOLOGY AND ETIOLOGY

The exact prevalence of CLD in children is not known. On an average, tertiary care hospitals in India manage 100 cases of CLD

per year. The results from a single center in USA show 522 children with CLD included in the liver waiting list: 294 (56%) were girls and 345 (66%) were below 1 year of age. The diagnoses were: 377 (72%) biliary atresia (BA), 54 (10%) alpha-1 antitrypsin deficiency, 40 (7.6%) cryptogenic cirrhosis, 33 (6.3%) autoimmune hepatitis (AIH), 11 (2%) type 1 tyrosinemia, 5 (1%) biliary hypoplasia and 2 (0.3%) Wilson disease. In contrast the most common causes of CLD as evident from three tertiary care centers in India are chronic hepatitis B infection and Wilson disease (**Table 3**). But we must remember that chronic hepatitis B may not show evidence of CLD in childhood except fibrosis on histopathology. Among the cholestatic liver disease, BA is common world over.

PATHOPHYSIOLOGY**Development of Fibrosis and Cirrhosis**

Fibrosis is the wound healing response to a variety of acute and/or chronic stimuli, including viral infection, toxins, metabolic disease, cholestasis and drugs. Fibrosis is associated with a number of pathological and biochemical changes leading to structural and metabolic abnormalities, as well as with increased hepatic scarring. Hepatic fibrosis develops due to an increase in fibrillar collagen synthesis and deposition along with insufficient remodeling. Cirrhosis lies at the extreme end of the pathological spectrum and is characterized by fibrosis, architectural distortion and conversion of normal liver architecture into abnormal nodules. Cirrhosis is representing a state of competing processes of cell-injury related inflammation leading to cell death (necrosis) or response to injury (fibrosis), and regeneration (nodule formation). If necrosis predominates with little regeneration, hepatocellular failure or synthetic liver failure occurs resulting in ascites and coagulopathy. If fibrosis and regeneration predominate, portal hypertension (PHTN) is the result. Fibrosis of portal tracts will cause increased resistance to portal blood flow precipitating PHTN. It also leads to compression of biliary structures: this architectural distortion decreases oxygen and metabolites reaching the hepatocytes which in turn leads to continued cell injury even after the original cause of insult is over.

Host and Genetic Predisposing Factors

Apart from gender and duration of exposure, ethnicity and host genetic factors are likely to influence disease progression and prognosis. For example, although, patients with chronic hepatitis C virus (HCV) infection may develop cirrhosis after 20–50 years but long duration of infection, male gender, and alcohol consumption with positive family history may play an important role in early cirrhosis due to HCV. *Angiotensinogen* is an example of a candidate gene that is involved in Caucasians with chronic HCV.

In autoimmune hepatitis, the anomalous presentation of human leukocyte antigen (HLA) class II in hepatocytes, causes

Table 1 Evidence of chronic liver disease in children

Clinical	Biochemical	Imaging (Ultrasonography/CT)	Histopathology
History	Synthetic dysfunction	Signs of cirrhosis	• Increased liver fibrosis
Recurrent jaundice	Low albumin	Increased echogenicity	• Presence of regenerative nodules
Abdominal distension, Altered sensorium,	Reversal of A:G ratio	Irregularity of hepatic (nodular) surface	• Collapse of the normal lobular architecture
Swelling over body	Elevated INR	Enlarged caudate lobe	
Upper gastrointestinal bleed	Impaired secretory function	Evidence of portal hypertension	
Physical findings	Elevated ammonia	Splenomegaly	
Firm sharp or shrunken liver with or without splenomegaly	Elevated bilirubin	Dilated splenoportal axis	
Cutaneous signs of liver disease	Hypersplenism	Reversal of portal flow	
Periumbilical collaterals	Thrombocytopenia + Leucopenia/	Presence of collaterals	
Evidence of free fluid	Anemia		

Table 2 Etiology of the chronic liver disease in different age groups

Classification Age-group	Parenchymal				Cholestatic
	Metabolic	Immunologic	Vascular	Infective	
< 1 year	Galactosemia, Tyrosinemia HFI	-	-	-	Biliary atresia PFIC types 2 and 1
1–5 years	Tyrosinemia, HFI GSD type 4	Autoimmune	HVOTO	-	PFIC types 2 and 1 BASD SSC
5–10 years	Wilson disease, HFI	Autoimmune	HVOTO	-	PFIC types 1 and 2
10–18 years	Wilson disease, Gaucher's disease	Autoimmune	HVOTO	HBV HCV	PSC, PFIC type 3

Abbreviations: HFI, hereditary fructose intolerance; PFIC, progressive familial intrahepatic cholestasis; GSD, glycogen storage disorder; HVOTO, hepatic venous outflow tract obstruction; BASD, bile acid synthetic defect; SSC, secondary sclerosing cholangitis; HBV, hepatitis B virus; HCV, hepatitis C virus; PSC, primary sclerosing cholangitis.

Table 3 Distribution of the common causes of childhood CLD in three tertiary care Indian centers

	AIIMS (n = 840) 2010	SGPGI (n = 85) 1997	ILBS (n = 353) 2014
Wilson disease	76 (9%)	18 (21%)	34 (9.6%)
Chronic viral hepatitis	238 (28.3%)	11 (13%)	118 (33.4%)
Chronic HBV	206 (24.5%)	NA	105 (29.7%)
Chronic HCV	29 (3.4%)	NA	13 (3.7%)
Metabolic liver disease	83 (9.9%)	16 (19%)	20 (5.7%)
Autoimmune liver disease	52 (6.2%)	3 (4%)	35 (10%)
HVOTO	55 (6.5%)	2 (2%)	16 (4.5%)
Cholestatic liver disease	32 (4.2%)	NA	88 (24.9%)
Biliary atresia			55 (15.5%)
PFIC			20 (5.7%)
Sclerosing cholangitis			12 (3.4%)
Allagile syndrome			1
Indian childhood cirrhosis	2 (0.2%)	2 (2%)	0
Cryptogenic liver disease	237 (28.2%)	34 (40%)	13 (3.7%)

Abbreviations: AIIMS, All India Institute of Medical Sciences, New Delhi; SGPGI, Sanjay Gandhi Postgraduate Institute, Lucknow; ILBS, Institute of Liver and Biliary Sciences, New Delhi; CLD, chronic liver disease; HBV, hepatitis B virus; HCV, hepatitis C virus; HVOTO, hepatic venous outflow tract obstruction.

cell-mediated immune responses against the host liver, leading to liver fibrosis. Similarly some reports suggest that in addition to gender, certain HLA-II alleles and genetic variations of tumor necrosis factor alpha (TNF- α) influence both susceptibility and disease progression in primary sclerosing cholangitis (PSC). Metabolic disorders such as hemochromatosis and Wilson disease are typically accompanied by chronic hepatitis and fibrosis. In hereditary hemochromatosis, the excessive absorption and accumulation of iron in tissues and organs including liver is related to mutations in the *HFE* (High-iron) gene. Wilson disease is a genetic disorder leading to copper accumulation in the liver due to mutations in the ATPase (ATP7B) that transports copper. Inborn errors of metabolism with their genetic predisposition would be discussed presented later in the laboratory work-up section.

Molecular Mechanism of Fibrosis

Several cell types like hepatic stellate cells (HSC), Kupffer cells and hepatocytes are involved in the pathogenesis of hepatic fibrosis. Molecular pathogenesis of hepatic fibrosis is depicted in **Figure 1**.

- Following injury to the hepatocytes, quiescent HSCs become activated and acquire a myofibroblast-like phenotype losing

their typical star-shape by increasing the expression of α -smooth muscle actin. They become proliferative, motile, profibrogenic, contractile and show abundant rough endoplasmic reticulum.

- Damaged hepatocytes release lipid peroxidation products, metabolites of drugs or hepatotoxins, as well as reactive oxygen species (ROS) (hydrogen peroxide, superoxide radical) and induce HSC activation.
- Activated Kupffer cells release two potent profibrogenic cytokines (TGF- β and platelet-derived growth factor) activating HSC further.
- Kupffer cell phagocytic activity generates large amounts of ROS that activate HSC and induce their fibrogenic potential. ROS also up-regulate the expression of critical fibrosis-associated genes such as *COL1A1*, *COL1A2*.
- Increased permeability due to disruption of the intestinal epithelial barrier, bacterial overgrowth and altered gut flora promote bacterial translocation. Decreased bile acid secretion and impaired intestinal motility in liver cirrhosis also contribute to bacterial overgrowth. In cirrhosis, entry of bacteria and bacterial products to the liver induces activation of Kupffer cells and HSC through toll-like receptors (TLRs).
- Matrix metalloproteinases (MMPs) are the main enzymes responsible for degradation of extracellular matrix (ECM) while TIMPs (tissue inhibitor of metalloproteinases) inhibit MMPs. The balance of MMP-TIMP balance is crucial for remodeling of ECM. Activated HSC also produce MMP1 and MMP13. Moreover, activated HSC upregulate the expression and synthesis of TIMP1 and TIMP2. The net result is the deposition of mature collagen fibers within the *space of Disse* and thus scarring.

Portal Fibrosis

In the fibrotic or cirrhotic liver, the composition of the ECM has some qualitative and quantitative changes in the periportal and perisinusoidal areas. The amount of fibrillar collagens and proteoglycans increases up to six times than in normal livers. This leads to loss of endothelial cell fenestrations, altered hepatocyte function and subsequent nonparenchymal cell damage. Apart from hepatic fibrosis, portal fibrosis is another important event happening concurrently in cirrhosis. There are three cell types which play a role in portal fibrosis:

- Portal fibroblasts which lie quiescent in normal liver, form onion-like configurations around biliary structures. They also acquire a myofibroblast phenotype, and cause early deposition of ECM in portal zones.
- Mesenchymal cells emerging from epithelial-to-mesenchymal transition (EMT) after injury, derived either from resident hepatocytes or from biliary epithelial cells. EMT could be

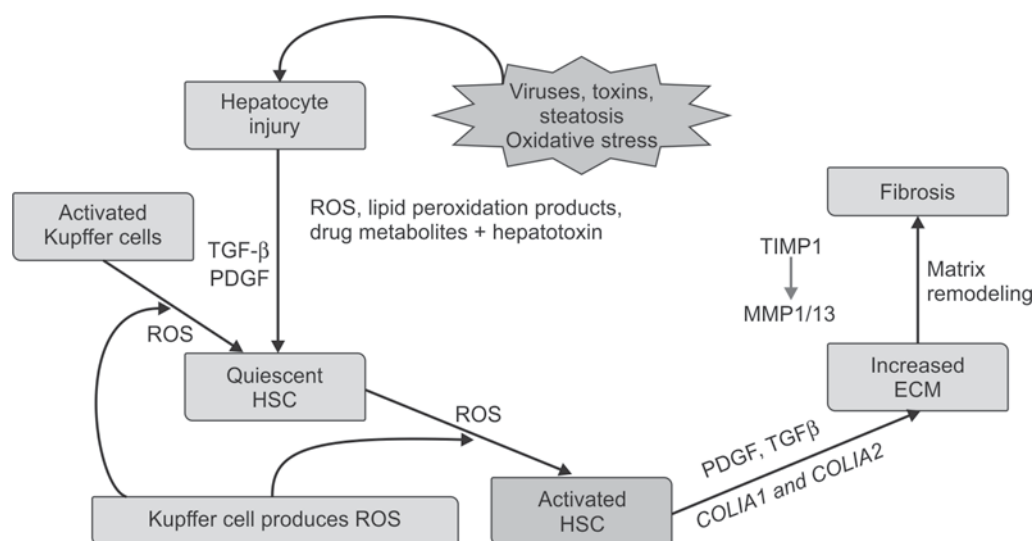


Figure 1 Molecular pathogenesis of fibrosis and cirrhosis

Abbreviations: HSC, hepatic stellate cells; ROS, reactive oxygen substances; ECM, extracellular matrix; PDGF, platelet-derived growth factor; MMP1, matrix metalloproteinase 1; TIMP1, tissue inhibitor of metalloproteinase 1; TGF-β, transforming growth factor-beta.

considered a mechanism participating in the pathogenesis of cholestatic liver disease.

3. Bone marrow-derived mesenchymal stem cells have the capacity to differentiate into hepatocytes, biliary epithelial cells, sinusoidal endothelial cells and even Kupffer cells.

CLINICAL FEATURES

Children with CLD or cirrhosis may present with failure to thrive, anorexia, easy fatigability and muscle weakness. Jaundice is sometimes present but not always noticeable. Alternatively, when CLD decompensates, jaundice, ascites, GIT hemorrhage, coagulopathy, spontaneous bacterial peritonitis, encephalopathy or hepatopulmonary syndrome (HPS) may signal the onset of the disease. Fever is occasionally present in decompensated CLD. Abdominal pain may be present and can be caused by peptic ulcer disease, gastritis, gastroesophageal reflux, or gallstones. Pallor could be due to anemia of CLD. Steatorrhea or fat malabsorption in CLD leads to malnutrition and rickets, often with pathological fractures. A history of epistaxis, hematemesis and hematochezia may be related to the coagulopathy of liver disease or to PHTN with esophageal and rectal varices. Hypersplenism is also a sign of portal hypertension.

Stigmata of Chronic Liver Disease

Amenorrhea, delayed puberty, pedal edema, ascites, clubbing or spider angiomas, palmar or plantar erythema and telangiectasia indicate the chronic nature and likelihood of hepatic fibrosis or cirrhosis. *Palmar erythema* is a nonspecific red discoloration of the palms and fingertips, indicative of a hyperdynamic circulation associated with cirrhosis (**Fig. 2A**). Skin flushing is frequently seen in cirrhotic patients due to increased circulatory vasodilators. In infants, palmar erythema may be accompanied by plantar erythema, which in older children is difficult to see due to keratinization of the soles. *Spider nevi* are telangiectasia consisting of a central arteriole with radiating small capillaries looking like a spider (**Fig. 2B**). These blanchable lesions, if more than 5 in number, are suggestive of CLD. Superficial distended capillaries (telangiectasia) on face (**Fig. 2C**) are common in CLD. Skin and extremity changes include jaundice, cyanosis, and pallor. Pallor may be present because of the anemia of CLD. Digital clubbing is seen due to chronic hypoxemia

secondary to HPS (pulmonary-systemic shunts and ventilation-perfusion mismatching) or in cases of biliary cirrhosis (**Fig. 2D**). Dupuytren contracture, gynecomastia, testicular atrophy and feminization are rarely seen in childhood. Pruritus is a common feature of cholestatic disorders which can be nocturnal or diurnal and affect the daily activities of the child. Scratch marks on the skin and shining nails are characteristic features of cholestatic liver disease, e.g., progressive familial intrahepatic cholestasis (PFIC) (**Fig. 2E**). All children of cholestatic liver disease should be carefully looked up for fat-soluble vitamin deficiency including toad-like skin, xerophthalmia, hematomas and rickets. Moreover PFIC type 1 and type 2 are short-statured children (**Fig. 2F**).

Nutritional Status of a Child with CLD

Table 4 shows the organic and nonorganic causes of malnutrition in CLD. Nutritional manifestations of cirrhosis include malnutrition, anorexia, malabsorption, steatorrhea, hypoalbuminemia, and fat-soluble vitamin deficiencies. Malnutrition is a common complication of liver disease, especially if the onset of liver disease is in infancy. CLD impairs the growth and pubertal spurt. Standard weight underestimates the extent of malnutrition in children due to associated ascites; the triceps skinfold thickness is more accurate assessment of patient's nutritional status. Vitamin A deficiency and rickets are commonly seen in all CLD and vitamin K deficiency can exacerbate other complications of cirrhosis, such as coagulopathy.

Ophthalmoscopic Examination

Cataract in infantile liver disease suggests the diagnosis of galactosemia. The characteristic greenish-brown ring at the periphery of the cornea called Kayser-Fleischer (K-F) ring is due to copper deposition in the Descemet membrane in Wilson disease. Visualization of K-F ring requires a slit-lamp examination, although sometimes it may be seen on torchlight. K-F rings may be present in 50% of the cases with liver disease and almost 100% of neurologic cases. The K-F ring may also be seen in patients with cholestatic liver disease. Sunflower cataract, though less common, is another ophthalmologic feature of Wilson disease. It is grayish-brown in color that may develop because of deposits of copper in the anterior and posterior lens capsule. Some of the lipid storage disorders (Gaucher disease and Niemann Pick type C) can present



Figures 2A to F (A) Palmar erythema; (B and C) Spider nevi and telangiectasia; (D) Clubbing in biliary cirrhosis; (E) Scratch marks in a patient with severe pruritus; (F) Short stature and rickets in a case with progressive familial intrahepatic cholestasis (PFIC2)

Table 4 Causes of malnutrition in childhood chronic liver disease

<ul style="list-style-type: none"> • Organic causes <ul style="list-style-type: none"> – <i>Reduced intake</i> <ul style="list-style-type: none"> ▪ Anorexia ▪ Early satiety: Compression of abdominal viscera by enlarged liver, spleen or ascites – <i>Malabsorption</i>: Reduced bile acids to the duodenum leading to malabsorption – <i>Alterations in metabolic milieu</i> <ul style="list-style-type: none"> ▪ Abnormalities in amino-acid and glucose metabolism ▪ Increased resting energy expenditure (Hypercatabolism) – <i>Endocrinal factors</i>: Reduced insulin-like growth factor-1 production by the liver • Nonorganic causes <ul style="list-style-type: none"> – Imposed restriction of fat and due to taboos, misbeliefs or improper education. – Restriction of protein intake during episodes of encephalopathy
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with cherry-red spot on fundus examination. Vertical gaze palsy is seen in Niemann Pick type C and oculomotor apraxia in Gaucher disease. *Posterior embryotoxon* on slit-lamp examination in a cholestatic child would suggest Alagille syndrome.

Abdominal Examination

A shrunken and nodular liver is definitely CLD but if liver is enlarged, then firm to hard consistency (with well-defined or sharp margins) would indicate CLD. The spleen is enlarged, especially in the setting of PHTN. Ascites may be present and often is associated with hypoalbuminemia. Splenomegaly, ascites, caput medusae, hemetemesis, malena, prominent or distended abdominal veins

(Fig. 3), or rectal varices suggest PHTN and singly could be the only evidences of CLD in some patients. When seen in an infant, splenomegaly and/or ascites could also suggest an intrauterine infection and metabolic liver disease. A hard enlarged liver is almost always seen in the infantile and childhood cholestatic liver disease. Infants and younger children with cholestatic liver disease (e.g., biliary atresia) rapidly progress to biliary cirrhosis and PHTN. Older children with cholestasis (e.g., PSC) have much slower progress.

Neurological Examination

Presence of mental changes, asterexis, prolonged relaxation of deep tendon reflexes and positive Babinski's sign can indicate central nervous system involvement in CLD. The encephalopathy may be obvious, or it may present in subtle forms such as deterioration of school performance, depression or irritability. To diagnose encephalopathy in younger children needs a high degree of suspicion as even inconsolable cry can be suggestive sign. For more details, the readers are referred to the chapter on encephalopathy.

CHARACTERISTICS OF VARIOUS CAUSES OF CLD

Wilson Disease

Clinical manifestations of Wilson disease are rarely apparent before age 5 years. It is more common in older children closer to or in second decade of life. Copper first accumulates in the liver followed by accumulation in nervous system, cornea, kidneys, and other organs and tissues. Hence, the liver involvement is seen during childhood, whereas ophthalmological and neurological involvement is more common in adolescents and adults. In the age group 5–10 years, over 80% affected children present with hepatic involvement and rest with neuropsychiatric symptoms; in the second decade, 50% each present with hepatic and neuropsychiatric symptoms; and in adulthood, 25% present with



Figure 3 Prominent abdominal veins indicative of portal hypertension. Umbilical hernia due to tense ascites

hepatic whereas 75% with neuropsychiatric symptoms. Malaise, anorexia, fatigue, abdominal pain, and nausea may precede the onset of jaundice and hepatic dysfunction. Cholelithiasis (copper-deficient cholesterol-rich stones), due to hemolysis, is relatively common in adolescents. Precocious puberty and recent poor school performance is suggestive of Wilson disease. Family history suggestive of neuropsychiatric disorder should be sought. Renal, endocrine, and hematologic involvement causes symptoms in the second decade. A combination of liver dysfunction and other organ system involvement, at any age, should alert to possibility of Wilson disease.

Autoimmune Hepatitis

There are two types of AIH depending upon the type of associated antibodies. *Type 1 AIH* is when antismooth muscle antibodies (Anti-SMA) are present which accounts for two-thirds of the cases. If anti-liver kidney microsomal (Anti-LKM 1) antibodies are present, then it is *Type 2 AIH*. Three-fourths of all AIH cases are girls in both types. History of fever and features of autoimmune disorders (skin rashes, arthralgia/arthritis, thyroiditis, autoimmune anemia, inflammatory bowel disease, vitiligo, insulin-dependent diabetes, and nephrotic syndrome) would indicate etiologic possibility of AIH. History of diarrhea with or without blood could be point to an association with celiac disease or inflammatory bowel disease, respectively. The most common presentation of AIH is episodes of relapsing jaundice (without typical prodrome), with progressive fatigue, anorexia and weight loss present for months to years. There may be flares and spontaneous remissions which delay the diagnosis. Fewer cases of AIH present with CLD and PHTN, with no history of jaundice. Because of variable presentation, all progressive liver disease should be investigated for AIH in childhood. Anti-LKM1-positive patients are younger and present more often with acute liver failure. About 20% of autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED) may have type 2 AIH.

Chronic Viral Hepatitis

Chronic HBV is a relatively infrequent cause of CLD in children as it mostly remains silent. Of these children, however, 3–5% develop cirrhosis while 0.01–0.03% may end up with hepatocellular carcinoma (HCC). History of exposure in the form of transfusions (e.g. thalassemia or hemophilia), tattooing, earpiercing, renal dialysis, surgery, hospitalizations or intravenous drug abuse could suggest HBV- or HCV-associated CLD. HBV-positive mothers can clear the HBV during pregnancy, so HBV-positive child may have resulted from vertical transmission in an HBV-negative mother. There is possibility of horizontal transmission if there is an HBV-

positive household contact. Although incidentally detected cases are more often seen, previous history of jaundice with preceding prodromal phase and arthritis suggests an episode of acute HBV. Like HBV, HCV infection is also more common in the background of hematological disorders, e.g., thalassemia or hemophilia where repeated blood transfusions are needed. Chronic HCV is a slowly progressive disease so they usually present with CLD in adulthood and is an uncommon cause of CLD in pediatric age group.

Hepatic Vein Outflow Tract Obstruction

Hepatic vein outflow tract obstruction (HVOTO) could be present in 7–8 % of all childhood liver disease. History of ascites with abdominal pain without jaundice would suggest vascular cause, e.g., HVOTO. Outflow tract obstruction explains the tender enlarged liver which is associated with these cases. Prominent or engorged abdominal and back veins, refractory (rapidly filling) ascites, pedal edema, enlarged liver or shrunken right lobe and compensatory enlargement of left lobe of liver, and mild or no splenomegaly despite other evidences of PHTN are the most prominent features of HVOTO. Majority of the cases of HVOTO at our center had a chronic form of presentation which is the most common presentation. Pedal edema suggests inferior vena cava (IVC) obstruction. History of deep vein thrombosis in the child and family may be present. History of intake of contraceptive pills in adolescent girls or anabolic steroids or herbal tea can be present in HVOTO.

Metabolic Liver Disease

These inborn errors of metabolism include liver disease as a clinical entity. Suggestive family history, consanguinity and dysmorphism with history of abortions or sib loss indicate metabolic liver disease (MLD). History of hypoglycemia, encephalopathy, seizures and failure to thrive in an infant or child would further suggest MLD. An infant with CLD presenting with hypoglycemia could be galactosemia or tyrosinemia type 1. These infants will decompensate with ascites, jaundice and rarely encephalopathy by the end of first 6 months of life. Infants with galactosemia may have cataract, seizures and associated *E. coli* sepsis. Children with tyrosinemia type 1 may have boiled cabbage body odor and refractory rickets. Hereditary fructose intolerance (HFI) should be suspected if there is history of vomiting and diarrhea following addition of fructose (in form of fruit juice or honey or sugar syrups, etc.) to the diet. Sometimes the timing of presentation could coincide with addition of medications in form of syrups and drops. Aversion to sweets in an older child would be present in fructose intolerance. Glycogen storage disorder (GSD) type 4 and Gaucher disease also may present as CLD. Children suffering with GSD type 4 may develop cirrhosis and PHTN in early childhood, whereas patients with Gaucher disease become cirrhotic in adolescence to adulthood. Gaucher disease presents with prominent splenomegaly, pallor and petechial rashes (due to bone marrow infiltration) and skeletal dysostosis in younger children (See Section 3 for details of Gaucher disease).

Drug-induced Liver Injury (DILI)

A small proportion of patients may develop CLD due to liver injury caused by various medications, herbs, or xenobiotics, with the exclusion of other common etiologies. Typically, the clinical history indicates a suspect drug with reasonable temporal association to the illness. Combination antituberculosis drugs were the most common cause, followed by the anticonvulsants, phenytoin and carbamazepine in a group of 39 Indian children and adolescents.

Cholestatic Liver Disease

Biliary cholestasis is the prominent finding in all the cholestatic diseases, mostly presenting with jaundice, pruritus,

hyperpigmentation, xanthomas and fat soluble vitamin (Vitamin A, D, E, K) deficiencies. Pruritus is a predominant symptom in certain cholestatic disorders like PFIC, Alagille syndrome and sclerosing cholangitis. Cholangitis presenting with fever, jaundice, pain abdomen and pale-colored stools is seen in postoperated BA, sclerosing cholangitis and structural defects (choledochal cyst type 4a and 4b and Caroli disease). Cholestatic liver diseases progress slowly to cirrhosis except those presenting in infancy (biliary atresia, subacute sclerosing cholangitis, progressive familial intrahepatic cholestasis).

Biliary Atresia

Biliary atresia without Kasai surgery proceeds to cirrhosis with PHTN in infancy and only 10% may survive up to 2–3 years of life. Among those operated, 20% may require liver transplantation in childhood. About 80% of children with BA with successful Kasai surgery would go through to adult life with the native liver, albeit with cirrhosis and PHTN. The operated cases of BA, who have repeated episodes of cholangitis, are more likely proceed to cirrhosis and PHTN.

Progressive Familial Intrahepatic Cholestasis

Progressive familial intrahepatic cholestasis refers to a group of autosomal-recessive cholestatic liver disorders of childhood. The estimated incidence varies between 1/50,000 and 1/100,000 livebirths. PFIC1 is due to defect in *ATP8B1* encoding the FIC1 protein which impairs the transport of bile constituents, e.g., phosphatidylcholine. PFIC2 is caused by defect in *ABCB11* encoding bile salt export pump (BSEP) protein. Defects in *ABCB4*, encoding multidrug resistance 3 protein (MDR3) impair biliary phospholipid secretion, resulting in PFIC3. PFIC1 and PFIC2 have onset in the early infancy. Onset of PFIC3 may be in late infancy or childhood or even during young adulthood.

The main clinical manifestations include cholestasis, pruritus and jaundice. PFIC patients usually develop fibrosis and end-stage liver disease before adulthood. PFIC 1 and PFIC 2 can be differentiated on the basis of some extrahepatic features which are associated with PFIC 1. The *ATP8B1* gene is expressed in various organs, including the liver, pancreas, kidney and small intestine, but is more highly expressed in the small intestine than in the liver. Therefore, it is thought to be also involved in the enterohepatic cycling of bile salts. This may also explain the chronic diarrhea present in a few children with PFIC1 which may worsen after liver transplantation. Other extrahepatic features associated with PFIC1 include persistent short stature, deafness and pancreatitis. These suggest a general cell biological function for *FIC1*. The phenotypic spectrum of PFIC3 ranges from neonatal cholestasis to cirrhosis in young adults.

Sclerosing Cholangitis

Sclerosing cholangitis are chronic cholestatic inflammatory diseases which cause obliterative fibrosis of the bile ducts, leading to biliary cirrhosis. Four clinical forms seen in children:

1. *Neonatal sclerosing cholangitis*: It is most probably an autosomal recessive disease. It presents as neonatal cholestasis, so not within the purview of this chapter.
2. *Primary sclerosing cholangitis*: PSC of unknown etiology is relatively infrequent in children with likely incidence 0.2 cases per 100,000 patient years. The largest pediatric PSC series include only 214 cases in all, and centers manage 2–3 cases per year. PSC is a slowly progressive disease of the older children and is very often associated with ulcerative colitis. Common presenting symptoms are pain in abdomen, jaundice and pruritus. Often it takes years for the biliary cirrhosis and PHTN to get established in childhood PSC.

3. *Secondary sclerosing cholangitis (SSC)*: SSC secondary to various diseases, including Langerhans cell histiocytosis (LCH), primary immunodeficiencies and acquired immunodeficiency syndrome. SSC is usually seen in young infants and children where the abnormal cells cause sclerosis of the bile ducts resulting in sclerosing cholangitis.
4. *Autoimmune sclerosing cholangitis (ASC)*: ASC has similar presentation as the AIH and is particularly frequent in pediatric age, where it is more common in girls, responds to immunosuppressive treatment and has a better prognosis than classical PSC.

CLASSIFICATION OF CIRRHOSIS

Two macroscopic (appearance of the liver as seen by the naked eye) types of cirrhosis have been described. However, a mixed pattern may also be seen: (a) *Micronodular cirrhosis* (< 3 mm nodules)—where the liver is usually enlarged with small nodules of uniform size. This is associated with drug, chronic hepatitis, chronic venous obstruction, hemochromatosis and chronic biliary disease; and (b) *Macronodular cirrhosis* (> 3 mm nodules)—where the liver is almost always shrunken with large bulging nodules. This is the common form seen in chronic viral hepatitis, chronic AIH and Wilson disease. Some of these causes may have mixed (micronodular and macronodular) picture.

DIFFERENTIAL DIAGNOSIS

Moderate to massively enlarged spleen, PHTN and normal liver functions go against the diagnosis of CLD. An ultrasound Doppler done in such a patient would decide whether the diagnosis is having extrahepatic portal vein obstruction (EHPVO) or noncirrhotic portal fibrosis (NCPF) (**Flow chart 1**). Liver histology in NCPF would show no evidence of cirrhosis or parenchymal injury. Hepatic venous portal gradient would be normal in both these disorders. Moderate to massively enlarged splenomegaly, with or without PHTN with history of recurrent cholangitis is suggestive of *congenital hepatic fibrosis*. This is an autosomal recessive inherited fibropolycystic disease defined histopathologically by a variable degree of periportal fibrosis and irregularly shaped proliferating bile ducts.

COMPLICATIONS OF CIRRHOSIS

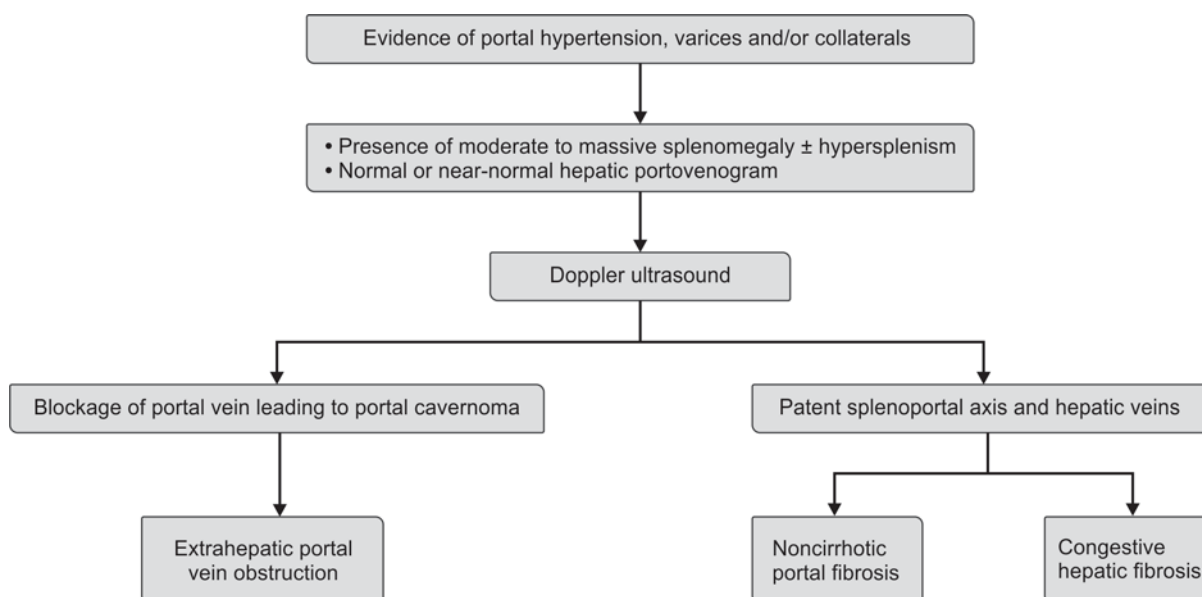
Since encephalopathy and PHTN with associated variceal bleed, ascites and spontaneous bacterial peritonitis are being detailed elsewhere, we have left them out of the present discussion.

Hepatopulmonary Syndrome

Hepatopulmonary syndrome is a triad of liver disease, intrapulmonary vascular dilatation and arterial hypoxemia. HPS is present in 9–20% of children with cirrhosis and PHTN. It can be asymptomatic or can present with growth retardation, cyanosis, dyspnea, platypnea, orthopnea, spider angioma or finger clubbing. PHTN causes bowel ischemia, increasing gut permeability and bacterial translocation of bacteria, which leads to the activation of VEGF-dependent signaling pathways and pulmonary angiogenesis.

Hepatorenal Syndrome

Hepatorenal syndrome (HRS) and acute kidney injury (AKI) are rare complications in pediatric CLD. Whereas AKI encompasses all etiologies (prerenal, renal and postrenal) which predispose to sudden acute deterioration in renal functions over 2 weeks, HRS refers to a specific type of prerenal failure, which develops secondary to intense renal vasoconstriction as a compensatory response to splanchnic vasodilatation secondary to PHTN. Among the two types of HRS identified: type 1 is acute and rapidly progressive developing after a precipitating event like

Flow chart 1 Portal hypertension with moderate to massive splenomegaly

GIT bleed or spontaneous bacterial peritonitis; whereas Type 2 is a slowly progressive form of renal failure associated with chronic ascites. In children it can be defined as oliguria (< 1 mL/kg/hour) with renal dysfunction (in the absence of usage of diuretics and other nephrotoxic drugs) and nonresponsive to albumin infusion. HRS is a reversible condition with poor prognosis for type 1.

LABORATORY WORK-UP

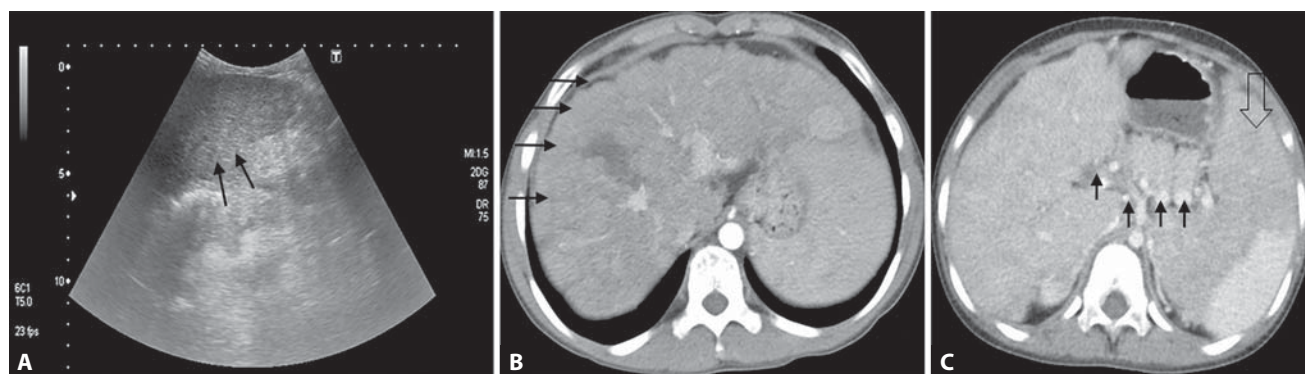
When the evidence for CLD has been found biochemically (as mentioned in **Table 1**) and on imaging (**Figs 4A to C**), liver biopsy gives further directions regarding the cause of the disease (**Fig. 5**). Synthetic liver dysfunction and elevated transaminases go in favor of parenchymal injury and elevated serum alkaline phosphatase (SAP) and/or Gamma glutamyl transferase (GGT) indicate cholestatic causes. In **Table 5**, the parenchymal causes of CLD in the different age groups have been discussed including the screening tests, confirmatory tests and the genetic testing of the various etiologies. **Table 6** discusses the causes of cholestatic CLD based on the GGT level being low or high and whether pruritus is part of the presenting feature or not.

MANAGEMENT OF CHRONIC LIVER DISEASE

General Management

Basic management of an infant or child with CLD is focused on: (1) nutritional support and rehabilitation, careful surveillance for growth and complications with subsequent management, and regular assessment for need for liver transplantation.

Nutritional support and rehabilitation An aggressive approach to nutritional support is essential in management of an infant or child with CLD as poor nutritional status is associated with poor brain growth, delayed mental development and susceptibility to recurrent infections. Pretransplant nutritional status also determines the outcome, speed of recovery and cognitive performance after liver transplantation. Nutritional goals and recommendations for infants and children with CLD are mentioned in **Table 7**. Vigorous growth monitoring is indicated in some patients, especially those who are candidates for liver transplantation, or those with severe cholestasis. Bolus dose of vitamins A (oral or intramuscular) and D (intramuscular) is indicated in cases with well-established features of xerophthalmia and rickets, respectively. Specific nutritional management for certain disorders is discussed in later sections.



Figures 4A to C (A) Ultrasonography of upper abdomen showing small shrunken liver with coarse echotexture (arrows); (B) Contrast-enhanced computerized tomography (CECT) of abdomen showing nodular liver surface; (C) CECT abdomen showing splenomegaly (open arrow) and presence of numerous splanchnic venous collaterals (arrows)

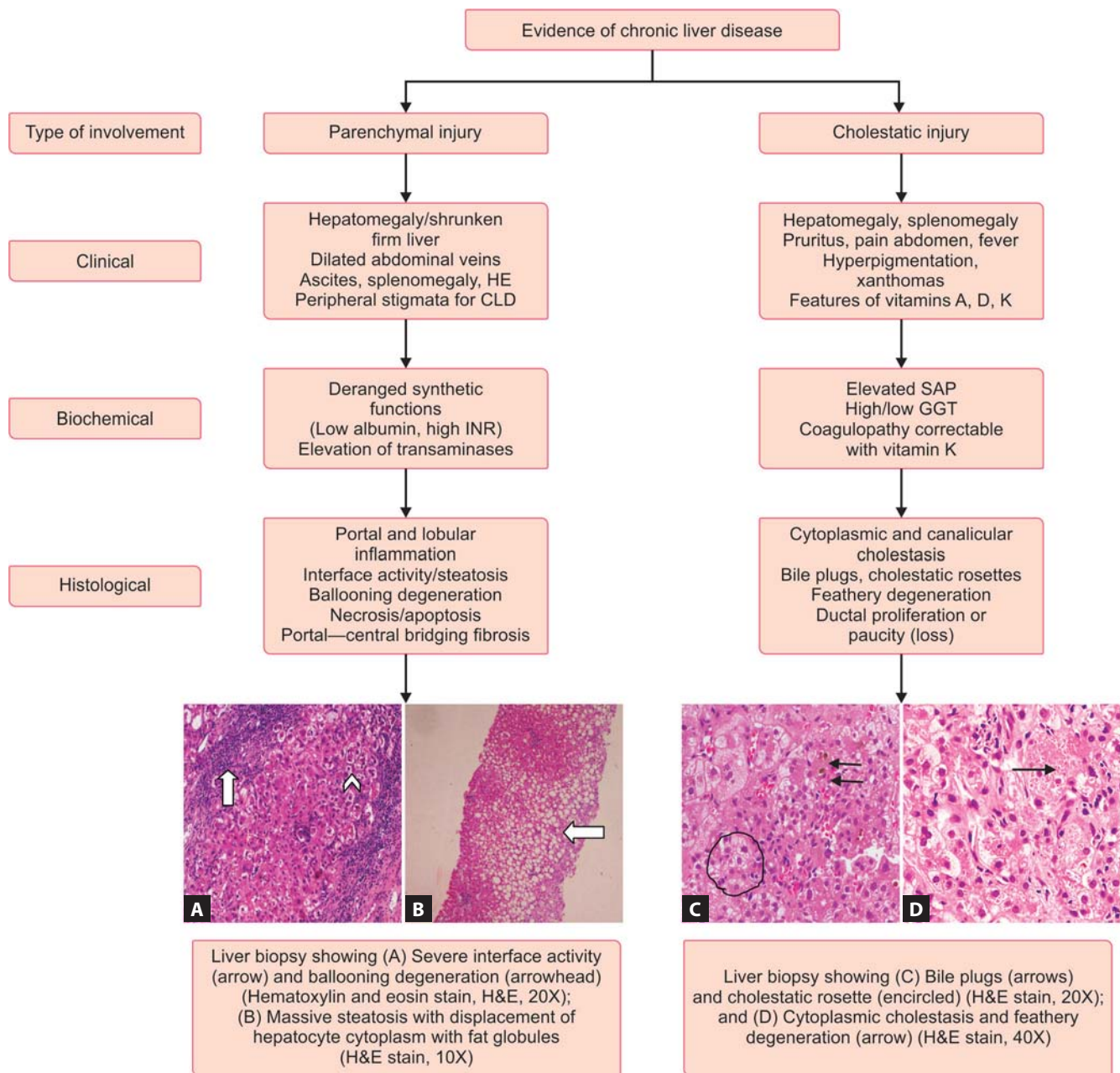


Figure 5 Approach to a child with chronic liver disease

Surveillance Surveillance strategies in infants and children with CLD are not well defined and some of these have been adapted from adult guidelines (**Table 8**). Screening UGIE should be early (~6 months) and more frequent in cases of BA where PHTN is known to be rapidly progressive. Alpha fetoprotein (AFP) should be done in cases with known predisposition for HCC like BA, PFIC-2, hepatitis-B, glycogen storage disease and tyrosinemia, and in the later, the surveillance should be more frequent (~3 monthly). Age-appropriate cut-offs for AFP should be considered suggestive. HRS should be looked for with every episode of infection (urinary tract, pneumonia, spontaneous bacterial peritonitis, sepsis), large volume paracentesis, diarrhea or vomiting.

Candidacy for liver transplantation At each follow-up, patients should be assessed both clinically as well as biochemically regarding candidacy for liver transplantation on the basis of

available severity scores (**Table 8**). A value of CTP > 7, MELD > 14 or PELD > 12 indicates candidacy for liver transplantation. Other indications in children may differ for the primary disease—severe excruciating pruritus, growth failure despite adequate nutritional rehabilitation, recurrent cholangitis, ascites which is rapidly filling or refractory to medical management, episode of SBP, two or more episodes of HE and development of HPS.

Ursodeoxycholic Acid

Ursodeoxycholic acid (UDCA) is a hydrophilic, tertiary biliary acid normally constituting small proportion (< 3%) of the human bile-acid pool. In the body, it is formed by 7-epimerization of chenodeoxycholic acid, thus making it more hydrophilic in nature. UDCA, being hydrophilic, replaces the toxic hydrophobic bile-acids from both the bile-acid pool as well as the hepatocellular membranes and improves bile-salt-dependent bile flow. It also facilitates bile

Table 5 Evaluation of childhood CLD with parenchymal liver injury

	Consider	Screening test	Confirmatory test/Further testing	Genetic testing
Parenchymal liver diseases				
< 1 year	Galactosemia	Positive urine NGRS	Low GALT assay	Gene located on 9p18 Mutations—N314D, Q188R
	Tyrosinemia	High AFP	High urine succinylacetone	Gene located on 15q25.1 Mutations—IVS12+5ga
1–3 years	Hereditary fructose intolerance (HFI)	Fructose tolerance test*	Low aldolase B assay	Gene located on 9q22.3 Mutations—A149P
	Tyrosinemia	As above	As above	As above
	HFI	As above	As above	As above
	Glycogen storage Disorder type IV	PAS-positive cytoplasmic inclusions in hepatocytes	Abnormal glycogen with fewer branch points ultrastructurally and histochemically	Gene located on 3p12
	Hepatic venous outflow tract obstruction (HVOTO)	Doppler for hepatic veins and IVC patency and flow	Contrast-enhanced CT or MR venography	Prothrombotic predisposition Janus-kinase 2 (V617F) Prothrombin (G20210A) MTHFR (C677T) Factor-V Leiden (R605Q)
> 3 years	Wilson disease	Ceruloplasmin < 20 mg/dL K-F ring on slit-lamp examination 24 hours Urine Copper > 40 µg/day	Liver copper (> 250 µg/g of dry weight) MRI brain	ATP7B gene located on 13q14 Mutations—H1069Q, p.C271, R778L, p.E122fs
	Autoimmune hepatitis	High IgG or reversal of A:G ratio Antibodies (ANA, SMA, LKM)	Liver biopsy Clinical and histological response to treatment	HLA-DR
	Chronic HBV	HBsAg + for > 6 months	HBeAg Anti-HBe HBV-DNA (Quant)	Resistant mutants of HBV Lamivudine M204V/I**, L180M Adefovir A181V, N236T Entecavir T184G/S, S202I, M250V
	Chronic HCV	Anti-HCV+	HCV-genotyping HCV-RNA (Quant)	IL-28/ITPA polymorphism [#]
Any age with splenohepatomegaly	HVOTO	As above	As above	As above
	Gaucher's	Gaucher cells (macrophages with wrinkled tissue paper appearance) in bone-marrow, liver and lymph nodes	Low acid-β-glucosidase	Gene located on 1q22 Mutations—N370S, L444P
	Niemann-Pick C	Foam cells (lipid-laden macrophages) within bone marrow and liver	Impaired cholesterol esterification and filipin staining in cultured fibroblasts	Genes located on 18q11-q12 (NPC1) and 14q24.3 (NPC2). > 130 mutations

* Following an oral fructose load, there is development of hypoglycemia, hypophosphatemia, hyperuricemia, hypomagnesemia and hypertriglyceridemia.

** YMDD mutation; [#] Polymorphism determines treatment responsiveness in genotype-1 hepatitis C.

Table 6 Evaluation of childhood CLD with cholestatic liver injury

<i>Presentation</i>	<i>Pruritus</i>	<i>Differentials</i>	<i>Supportive findings or tests</i>	<i>Confirmatory tests</i>	<i>Genetic linkage</i>
Low GGT	++	Progressive familial intrahepatic cholestasis (PFIC) type 1/2	Growth failure; Low biliary BA 1 → Extrahepatic features (diarrhea, pancreatitis, deafness); bland cholestasis on liver biopsy 2 → Gallstones; giant cell hepatitis on liver biopsy	1 → Coarse granular bile (Byler's) on electron microscopy 2 → Deficient immunostaining for BSEP	1 → ATP8B1 (or FIC1) gene on chr 18q21-22 2 → ABCB11 (or BSEP) gene on chr 2q24
	±	BASD	Steatorrhea, growth failure Low serum BA	Abnormal bile-acid conjugates on LSIMS/GC-MS	Mutations in HSD3B7 gene
High GGT	+++	Alagille syndrome	Facial dysmorphism, slit-lamp examination for posterior embryotoxon, X-ray spine for vertebral defects, peripheral pulmonary artery stenosis (murmur in axilla or back)	Liver biopsy—Paucity of bile ducts (Bile duct: Portal tract < 0.4)	Mutations in Jagged1 (on chr 20p12.1-p11.23) and NOTCH2 genes (on chr 1p13-p11)

Contd...

Contd...

Presentation	Pruritus	Differentials	Supportive findings or tests	Confirmatory tests	Genetic linkage
	+++	Secondary sclerosing cholangitis	Seborrheic dermatitis, Otorrhea, bone lesions (skull, vertebra, pelvis), lymph-node enlargement, cytopenia, exophthalmos, diabetes insipidus	Look for Langerhans cell histiocytosis (CD1a and 207 positive cells with Birbeck granules)	Nil
	+	PFIC 3	Gall stones early portal HTN	Deficient immunostaining for MDR3	Mutations in ABCB4/MDR3 gene (on chr 7q21)
	±	Primary sclerosing cholangitis	Positive ANA/p-ANCA Evidence of cholangitis	MRCP—Beading, dilatations, strictures Liver biopsy—Ductal lesions, portal edema, fibrosis, sclerosis (onion-skinning)	Presence of HLA-DRB3-0101 allele

Table 7 Nutritional recommendations for infants and children with CLD

• Energy: 125% of RDA based on weight for height at 50th percentile. Consideration should be given to night-time or continuous nasogastric feeds or, in specialized settings, gastrostomy feeds.	
• Fat: Medium chain triglycerides (MCT) should comprise 60–70% of total fat intake. MCT should be supplemented in a dose of 1–2 mL/kg/day. Corn-oil or safflower oil should be added in the diet to prevent essential fatty acid deficiency.	
• Protein: 2–3 gm/kg/day. During periods of hepatic encephalopathy, the protein intake needs to be reduced to 0.5–1.0 gm/kg/day, with restriction of animal protein and adequate supplementation of branched chain amino-acids.	
• Fat-soluble vitamins: 3–5 times of RDA.	
– Vitamin-A:	5,000–25,000 U/day orally
– Vitamin-D:	3–5 µg/kg/day of 25-OH-D or 0.05–0.2 µg/kg/day of 1,25-OH ₂ -D
– Vitamin-E:	25–200 IU/kg/day as α-tocopherol or 15–25 IU/kg/day of TPGS
– Vitamin-K:	2.5–5.0 mg twice a week to daily dose orally as menadione (or phytonadione)
• Water-soluble vitamins: 1–2 times of RDA	
• Minerals and Trace elements	
– Calcium	25–100 mg/kg/day as CaCO ₃ tablets or syrups orally (max 800–1,200 mg/day)
– Phosphorus	25–50 mg/kg/day orally (max 500 mg/day)
– Magnesium	1–2 mEq/kg/day of MgO orally, or 0.3–0.5 mEq/kg/day of MgSO ₄ (50%) IV (slow)
– Zinc	ZnSO ₄ 1–2 mg/kg/day orally for 2–3 months
– Iron	5–6 mg/kg/day of elemental iron

salt-independent bile flow by direct effect on cholangiocyte Ca²⁺-activated Cl[−] secretion, resulting in bicarbonate-rich choleresis. Apart from these choleretic actions, UDCA also has hepatoprotective effects—stabilization of hepatocellular membranes, improvement of mitochondrial oxidative phosphorylation and prevention of mitochondrial membrane permeability transition, the later effect helps in protecting against both apoptotic as well as necrotic cell injury. It also reduces expression of HLA-1 antigens on hepatocytes, thus having immunomodulatory properties. It is used in a dose of 10–30 mg/kg/day (maximum 1,500 mg/day in 2–3 divided doses) and has been shown to improve biochemical tests and pruritus, and reverse fibrosis and liver injury. Important side effect is diarrhea. The drug is poorly absorbed in case of severe cholestasis and there is concern of increased conversion to hydrophobic lithocholic acid, which is known to have carcinogenic potential.

Treatment of Pruritus

General measures include cool baths, moisturizers, topical steroid creams, topical anesthetics, antihistaminics and sedatives. Fingernails should be trimmed; and in young children at night, long-sleeve shirts should be worn and hands should be covered with stockings. Targeted approach is directed toward the possible etiopathogenetic theories related to development of pruritus—

choleretics (UDCA, phenobarbitone, removal of pruritogens (bile-acid sequestrants like cholestyramine, colestipol, colesvelam; plasmapheresis and extracorporeal albumin dialysis), alteration of metabolism of pruritogens (rifampicin); or modulation of central or peripheral pruritogenic signals (opioid antagonists, serotonergic). With failure of medical management, surgical options are considered—partial external (PEBD) or internal biliary diversion (cholecysto-jejuno-colonic anastomosis). Theoretical basis for diversion surgery is interruption of enterohepatic circulation of bile-acids, thus causing an overall reduction of bile-acid pool. Diversion surgery results in improvement in pruritus and growth, and resolution of fibrosis, but is advisable only before cirrhosis has set in, otherwise the child is considered for liver transplant. A step-wise management is advised for the management of pruritus (**Table 9**).

Immunization

All the infants and children with CLD need to be immunized against hepatitis-A and B. The decision should preferably be taken after testing for immunoglobulin G (IgG) antibodies (antihepatitis-A and antihepatitis-B) titers. Candidates awaiting liver transplant should receive all live (polio, measles, mumps, rubella, BCG, varicella) and inactive vaccines (diphtheria, pertussis, tetanus, *Haemophilus influenzae* B, pneumococcal influenza and typhoid).

Table 8 Surveillance of infants and children with CLD

Evidence of portal hypertension (Varices or PHG on UGIE)	
No varices	UGIE every 1–2 years
Small varices (< 5 mm in size), no RCS	UGIE every 6 months–1 year
Large varices (> 5 mm in size) or small varices with RCS	
Decompensation —Presence of any one of the following:	OPD visit every 3 months
<ul style="list-style-type: none"> Increasing jaundice Development or worsening of pre-existing ascites Hepatic encephalopathy Variceal bleed 	
Hepatopulmonary syndrome	Every 3–6 months
Orthodeoxia (difference in supine and upright SpO ₂ > 4%) PO ₂ and A-aO ₂ on ABG (at room air)	
Saline contrast echocardiography (when above two tests abnormal)	
Hepatorenal syndrome/Acute kidney injury	During and after each predisposition
Patients on diuretics	Every 1–3 months
Malignancy (Hepatocellular carcinoma)	AFP and ultrasound 6 months
Candidacy for liver transplantation	Every FU 3–6 months
CTP score	Bilirubin, Albumin, Ascites, HE and INR
PELD score (≤ 12 years)	Bilirubin, Albumin, INR, Age < 1 year, Growth
MELD score (≥ 12 years)	Bilirubin, Creatinine, INR, Need for hemodialysis within 2 weeks
MELD-sodium (MELD-Na)	Incorporation of serum Na into MELD score

MANAGEMENT OF COMPLICATIONS

Ascites, spontaneous bacterial peritonitis, HE, variceal bleed, HPS and HRS are various complications of CLD seen in children. As the first four complications are discussed elsewhere in this Section, we are discussing here the remaining two complications.

Table 9 Management algorithm for pruritus in children

Action	Drug	Dose (mg/kg/day)	Frequency/day	Side effects/Precautions
Start	UDCA	10–30	2–3	Diarrhea
	+ Hydroxyzine	0.5–1	1–2	Sedation
Add	Cholestyramine	250–500	2–4	Fat-soluble VAD, unpalatability, steatorrhea
Add Rifampicin	Rifampicin	5–10	1–2	Hepatotoxicity
Add/Substitute	Naltrexone	0.25–0.5	1–2	Opioid withdrawal
Consider adding/ substituting	Ondansetron	0.45–0.9	2	Constipation
	Phenobarbitone	5–10	2	Sedation
	Cyproheptadine	0.2–0.4	2	Sedation
Nonsurgical treatments		Surgical management		
Plasmapheresis		Cirrhosis absent		Cirrhosis absent
Extracorporeal albumin dialysis		Biliary diversion		Liver transplantation
Ultraviolet-B radiation		External or internal		

Management of Hepatopulmonary Syndrome

Bedside screening for HPS is done with demonstration of orthodeoxia—difference of > 4% in oxygen saturation on pulse oximetry [or PO₂ on arterial blood gas (ABG)] between lying down and upright positions. The alveolar-arterial oxygen gradient (A-aO₂) is increased (>15 mm Hg) with or without hypoxemia. Confirmation is done by demonstration of air bubbles after 3 cardiac cycles on left side of heart after injection of agitated saline intravenously (saline contrast echo) along with exclusion of cardiopulmonary disease. Shunt fraction is quantified on Technetium-99m-labeled macroaggregated albumin (^{99m}Tc-MAA) scan depending on the proportion of radio-labeled isotope reaching brain in comparison to that retained in lungs. Various drugs have been used in adults but with a limited role. Liver transplant reverses HPS in 80% of cases, although those with severe hypoxemia may have delayed recovery and risk of mortality.

Management of Hepatorenal Syndrome and Acute Kidney Injury

It is diagnosed in a cirrhotic patient with an acute rise in creatinine level (> 1.5 mg/dL, or doubling over 2 weeks period) with absence of response (not > 50% reduction) to volume expansion with albumin 1 g/kg for 2 days and to diuretic withdrawal, along with absence of shock, usage of nephrotoxic drugs or intrinsic renal disease. Key points in management are stopping of diuretics and nephrotoxic drugs; and initiation of antibiotics, albumin and vasoconstrictors. Vasoconstrictors most commonly used in adults are terlipressin and norepinephrine. However, the definitions as well as management are not well defined in the pediatric age-group. AKI and HPS can be prevented by preventing variceal bleed with usage of β-blockers.

DISEASE-SPECIFIC MANAGEMENT

Treatment of Wilson Disease

Management of Wilson disease is centered on attaining a negative copper balance with usage of lifelong chelators and zinc. Liver transplantation, which corrects the underlying defect, is reserved for severe cases with new Wilson index (NWI) score ≥ 11 (See Chapter 37.7). Recently questions have been raised regarding the efficacy of NWI. Approach is individualized depending on the severity of symptoms and whether predominantly hepatic or neurologic involvement.

Chelators Various chelators used for achieving cupriuresis are described in **Table 10**. The most commonly used is D-penicillamine, which is supplemented with pyridoxine (25 mg/

Table 10 Drugs used in the treatment of Wilson disease

Drug	D-Penicillamine	Trientine	Ammonium tetrathiomolybdate	Zinc
Mode of action	Chelator, induces cupruria	Chelator, induces cupruria	Chelator, induces cupruria	Blocks copper absorption
Dose	Initiation phase: 20 mg/kg/day in 2–3 divided doses (maximum 1,500 g/day) Maintenance phase: 25–50% of dose	20 mg/kg/day in 2–3 divided doses Maintenance phase: 25–50% of dose	(dose not defined for children)	150 mg/day in 3 divided doses
Side effects	Fever, rash, proteinuria, nephritic syndrome, aplastic anemia, lupus	Gastritis, loss of taste, skin rash	Anemia, neutropenia Aplastic anemia	Gastritis, Zinc toxicity, Hepatotoxicity
Neurological worsening	10–20%	10–15%	Rare	Nil or very rare
Precautions	Gradual escalation of dose in neurological WD. 1 hour before or 2 hours after meals	Forms toxic complex with iron. 1 hour before or 2 hours after meals	Investigational	1 hour before or 2 hours after meals
Tests for monitoring efficacy	<i>Initiation phase:</i> 24 hours; Urinary Cu excretion as 200–500 mcg/day as target Non-Cp-bound Cu < 20 mcg/dL <i>Maintenance phase:</i> Non-Cp-bound Cu < 10 mcg/dL	Same as for D-penicillamine	Same as for D-penicillamine	<i>Initiation phase:</i> 24 hours; Urinary Cu excretion 75 mcg/day as target <i>Maintenance phase:</i> Non-Cp-bound Cu < 10 mcg/dL
Tests for monitoring side effects	Hemogram, urine for albuminuria, skin examination	Hemogram, iron studies	Hemogram	Serum zinc levels

day). The risk of neurological worsening has been described up to the tune of 10–50% and is related to sudden release of copper from the basal ganglia. Following adequate chelation, liver synthetic functions recover and there is improvement in clinical signs, such as jaundice and ascites typically during the first 2–6 months of treatment. Noncompliance to chelation leads to significant progression of liver disease in another 1–12 months needing liver transplantation.

Zinc Zinc induces intestinal metallothionein, which has greater affinity for copper than for zinc, preferentially binds copper present in the enterocytes and inhibits its entry into the portal circulation. Copper, thus bound, is not absorbed but is lost into the feces. Zinc therapy alone is helpful in cases with clinically as well as biochemically silent WD (asymptomatic cases detected on family screening), and is also recommended in those with neurological WD, where there is risk of neurological deterioration with chelators.

Combination treatment For patients who present with decompensated CLD, combining zinc with D-Penicillamine has become a popular treatment strategy despite a lack of extensive validation. The two types of treatments must be temporally dispersed through the day, with at least 4–5 hours between administration of the two drugs, or else they may neutralize each other.

Low-copper diet Patients with Wilson disease should remain life-long on a low-copper diet with elimination of organ meats, shellfish, nuts, chocolate and mushrooms. In case of concerns of high copper content in drinking water system, a copper-removing device should be installed in the plumbing system. Response to treatment is assessed clinically and biochemically in terms of resolution of jaundice, hemolysis and ascites, reduction in transaminases, improvement in international normalized ratio (INR) and albumin, and attainment of negative copper balance.

Liver transplantation Liver transplantation in Wilson disease is indicated in cases with fulminant presentation or those with decompensated end-stage liver disease unresponsive to medical therapy. In cases with predominantly neuropsychiatric involvement, indications for liver transplantation could be mild neurological involvement which could reverse with time after transplantation.

Treatment of Autoimmune Hepatitis

Immunosuppression remains the mainstay of therapy in cases with AIH. Children have more severe disease in comparison to adults perhaps because of frequent delays in diagnosis and also because of concurrent other autoimmune process. There are two different schools of thoughts—first one administer steroids alone, whereas the second one combines this with azathioprine right from the beginning (**Fig. 6**). The former regimen can be used in presence of severe cytopenia or thiopurine methyl transferase (TPMT) deficiency and pregnancy. More than 85% of children who receive steroids alone ultimately require addition of azathioprine. Although an 80% decrease of transaminases is seen within 6 weeks of initiation of immunosuppression, complete normalization may take months. Relapse while on treatment is seen in 40% of children with AIH and requires a temporary increase in dose of steroids. About 10% of cases respond either to mycophenolate mofetil, cyclosporine or tacrolimus. In children, it is often unsuccessful to withdraw immunosuppression in type-2 AIH.

Treatment of Chronic Hepatitis-B

The aim of management in children with cirrhosis related to hepatitis-B is to reduce the viral burden as low as possible with the use of antivirals irrespective of the levels of ALT or DNA or histological activity. Interferon preparations are contraindicated once cirrhosis has set in as they may precipitate decompensation. Long-term oral nucleoside analogues, like

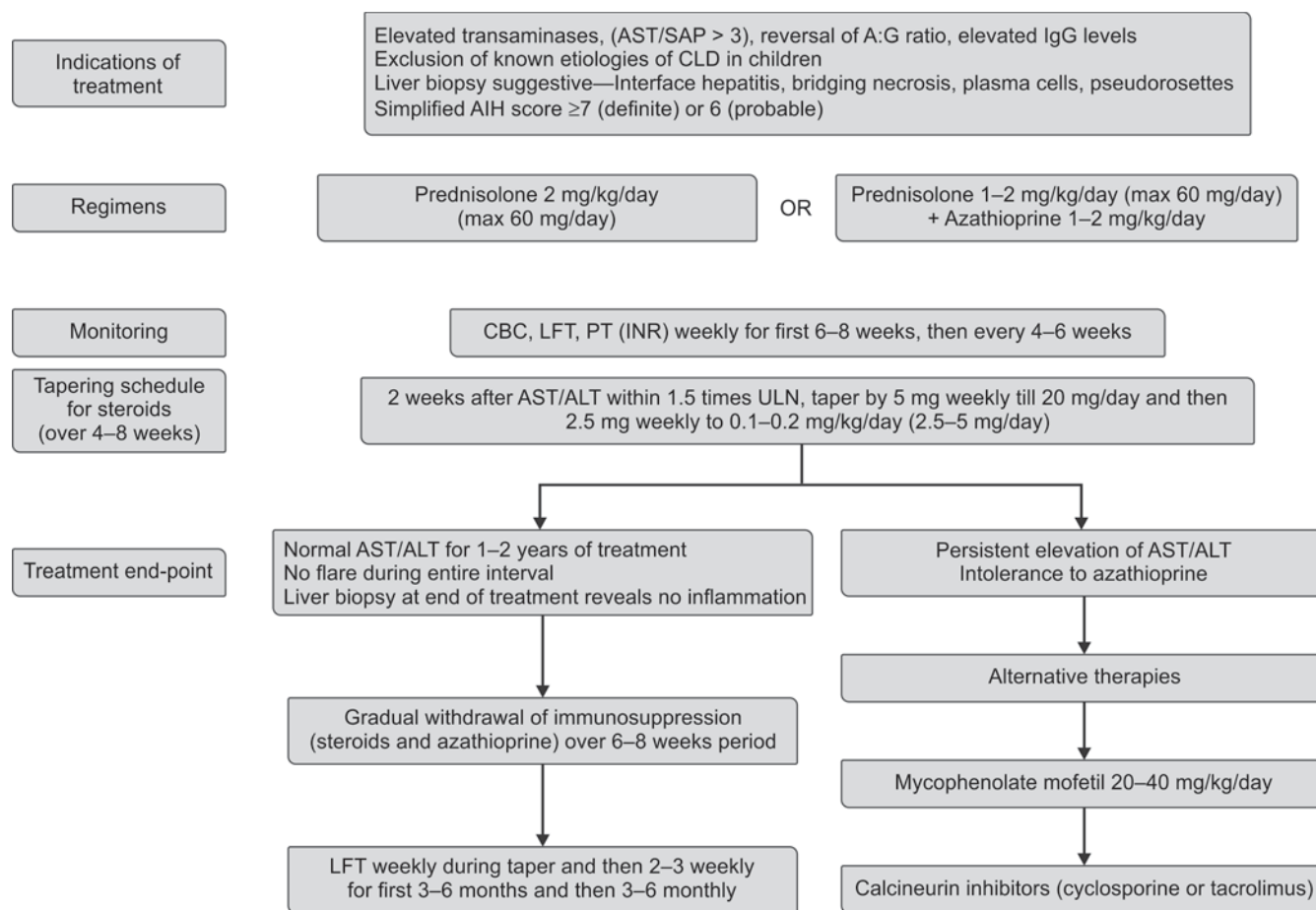


Figure 6 Treatment regimes for autoimmune hepatitis

lamivudine, adefovir, entecavir or tenofovir may be tried in these children.

Treatment of Metabolic Disorders

Some of the metabolic disorders like galactosemia and HFI can be well controlled by dietary restrictions. Elimination of galactose from the diet of children with galactosemia results in improvement of liver synthetic functions (prothrombin time and albumin) within a week, resolution of symptoms (like diarrhea, vomiting, seizures, ascites and cataract), normalization of growth and an overall improved survival. However, long-term sequels in the form of mental retardation, neurologic disorders, ovarian failure and growth inhibition continue to occur among survivors due to endogenous production and presence of minute amounts of galactose in all foods. Similarly, exclusion of fructose, sucrose and sorbitol in HFI leads to dramatic clinical and biochemical recovery. Younger infants recover more slowly from fructose exposure than older infants and children.

Tyrosinemia is difficult to treat with diet alone as restriction of essential amino-acids like tyrosine and phenylalanine interferes with the growth of the child. On subsidence of the acute phase, phenylalanine and tyrosine are provided in a restricted manner. Nitisinone or NTBC [2-(2-nitro-4-trifluoromethyl benzoyl)-1,3-cyclohexanedione] inhibits 4-hydroxy phenylpyruvate dioxygenase, which is an enzyme upstream in the tyrosine

metabolism pathway and, thus, the drug prevents formation of toxic metabolites. Nitisinone is administered in a dose of 1 mg/kg/day in divided doses with a target to maintain complete absence of detectable plasma and urine succinylacetone. Its usage has been shown to prevent acute hepatic and neurologic crises and avert need for liver transplantation when introduced within 1 month of age.

Treatment of Cholestatic Disorders

The management of cholestatic disorders like PFIC and PSC is concentrated on management of pruritus (*See above*). However, medical management does not prevent the progression of hepatic disease or resolution of extrahepatic manifestations. Liver transplantation is indicated in cases with intractable pruritus, growth failure despite adequate nutritional rehabilitation and recurrent cholangitis. SSC requires treatment for the associated disorder, e.g., LCH or primary immunodeficiencies. Certain cholestatic disorders like bile acid synthetic defects are reversible by medical management—primary bile acid therapy replacement in these disorders in the form of oral chenodeoxycholic acid (125–250 mg/day) and cholic acid (10–15 mg/kg/day, maximum 250 mg/day) results in clinical and biochemical recovery and transplant-free long-term survival.

IN A NUTSHELL

1. Definition of CLD based on duration is not practical for infants and children. Clinical, biochemical, radiological and histopathological evidences can be used to identify CLD.
2. CLD is classified into *Parenchymal type* and *Cholestatic type*.
3. The most common causes of parenchymal CLD are metabolic liver disease in the west and chronic HBV and Wilson disease in India.
4. The most common cause of cholestatic CLD is BA world over.
5. Hepatic stellate cells, Kupffer cells and hepatocytes are involved in the pathogenesis of hepatic fibrosis. Following injury to the hepatocytes, quiescent HSCs become activated, proliferative, motile, profibrogenic and contractile.
6. Among the complications of CLD, HPS is more frequent in children. HRS is uncommonly associated with childhood CLD.
7. Basic management of an infant or child with CLD is focused on nutritional support and rehabilitation, careful surveillance for growth and complications with subsequent management, and regular assessment for need of liver transplantation.
8. Management of Wilson Disease aims at attaining a negative copper balance with lifelong usage of chelators and zinc.
9. Combination therapy with steroids and azathioprine have good efficacy in treating AIH.
10. Some of the metabolic disorders like galactosemia and HFI can be well controlled by dietary restrictions. Tyrosinemia needs Nitisone and dietary elimination of tyrosine and phenylalanine.

MORE ON THIS TOPIC

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Chapter 37.9

Hepatic Encephalopathy

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Hepatic encephalopathy (HE) refers to a variety of reversible neurologic abnormalities seen in patients with liver diseases (mainly cirrhosis and liver failure). HE depends on three factors: (1) portosystemic shunting; (2) alterations in the blood-brain barrier; and (3) the interactions of toxic metabolites with the central nervous system (CNS).

This chapter will give a global overview of the presentation and management of hepatic encephalopathy in children. As HE is an important component of acute of liver failure (ALF), there will be considerable overlap in the management of both. ALF and chronic liver diseases (CLD) will be dealt separately elsewhere in the hepatobiliary section. HE in mitochondrial hepatopathies, urea cycle defects, Reye syndrome and congenital portosystemic shunts are rare but important disorders in children. These will be briefly elaborated at the end of this topic. Most studies on HE are adult-based and their experience is extrapolated to children.

PATHOPHYSIOLOGY

Exact pathophysiology is not well understood. A few hypotheses are discussed.

Ammonia Hypothesis (Acute Liver Failure Model)

Altered ammonia metabolism is a well-accepted postulation, depicted in **Figure 1**. Ammonia is produced by gut bacteria by converting glutamine to glutamate by enzyme glutaminase. About 80% of ammonia is usually removed from the portal vein blood in its *first pass* from the gut and detoxified in liver through urea cycle. The remaining 20% is removed primarily by the kidneys, in which the ammonia is protonated and excreted as a means of maintaining systemic acid-base balance. Muscle tissue also can absorb and metabolize ammonia. The brain also can take up ammonia and

detoxify it, mostly by production of glutamine, which then is metabolized to α -ketoglutarate.

In liver diseases there is abnormal handling of ammonia due to portosystemic shunting, parenchymal necrosis and muscle wasting. Additionally a state of respiratory alkalosis causes kidneys to retain the ammonia. A defective blood brain barrier (BBB) occurs due to endothelial dysfunction secondary to cytokines from inflammation. Contributory factors like hypokalemia, metabolic alkalosis and superimposed sepsis allow toxic metabolites to interact in the brain. Ammonia causes excitation by reduced inhibition of CNS and thus decreases the seizure threshold. In addition, the excess ammonia coupled with glutamate forms glutamine with the help of glutamine synthetase. Astrocytes swell up due to the excess glutamine and causes cerebral edema further worsening the encephalopathy.

Animal protein and blood in gut are rich sources of ammonia. Delayed intestinal transit by ileus, hypokalemia and constipation cause stasis and allow bacteria to produce more ammonia. The ammonia model also explains the encephalopathy encountered with urea cycle defects, organic acidemias, mitochondrial hepatopathies, congenital portosystemic shunts and Reye syndrome.

Other Hypotheses

Other toxic metabolites that contribute to HE are mercaptans, short and medium chain fatty acids (produced by gut bacteria) and increased gamma-aminobutyric acid (GABA) activity by neurosteroids. CNS inhibition contributes further by benzodiazepines (endogenous or as sedative drug). Decreased plasma branched chain amino acids (BCAA) levels allow aromatic amino acids (AAA) to influx through the BBB and produce *false neurotransmitters* like tyramine, octopamine and tryptamine (instead of true neurotransmitters: dopamine, norepinephrine and serotonin) cause HE.

Pathophysiology in Cirrhosis

Florid cerebral edema, intracranial hypertension and seizures are rarely seen in cirrhotics due to pre-existing cerebral atrophy and various compensatory mechanisms that are not present in acute liver failure. Manganese accumulation in basal ganglia in particular is seen in cirrhotics with extensive portosystemic shunts.

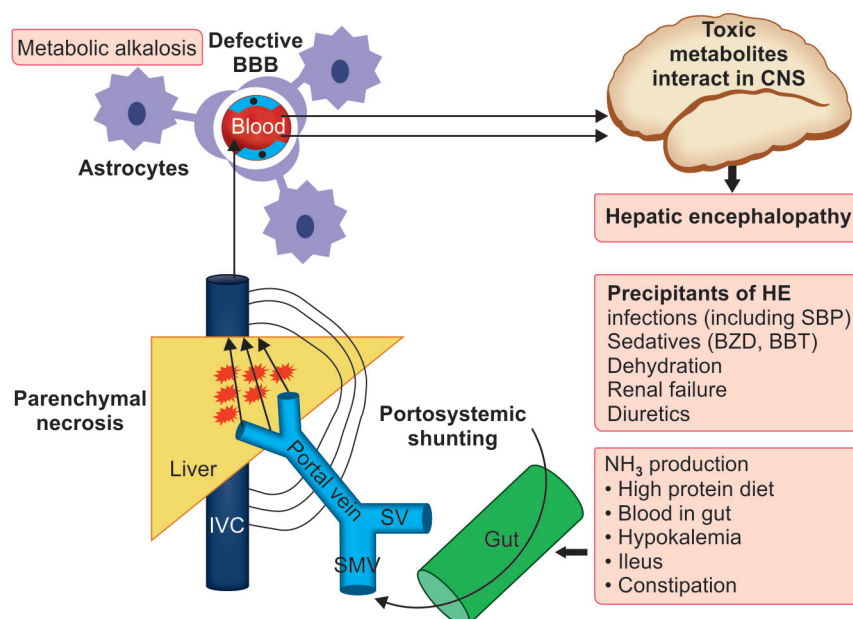


Figure 1 Pathophysiology of hepatic encephalopathy

Abbreviations: SBP, spontaneous bacterial peritonitis; BZD, benzodiazepines; BBT, barbiturate; NH₃, ammonia; SV, splenic vein; IVC, inferior vena cava; BBB, blood brain barrier; CNS, central nervous system.

DIAGNOSIS

The modified staging of HE is shown in **Table 1**. In smaller children, neurological signs are difficult to be elicited. Stages I and II are difficult to differentiate as they have similar clinical manifestations. Clinical assessment of staging in children includes constructional apraxia in stages I and II. Simple, age-related tasks are useful tools for the day-to-day assessment of inattentiveness and apraxia. In older children or adolescent, subtraction of serial sevens, recall of events, writing and figure drawings are appropriate tasks that can be asked to repeat daily in order to assess early encephalopathy. Younger children may be asked to color a figure in a simple coloring book while ward rounds are being completed. On the physician's return to the patient's bedside, it may be found that the task is not completed (inattentiveness) or that the once excellent *colorer* has scribbled far outside the lines (constructional apraxia). Handwriting may worsen which may be confirmed by the mother. The conventional drawing of a five-point star practiced in older children may not be expected till the child is 8–9 years of developmental age. Instead the child may be asked to draw simple shapes that are fine motor developmental age-appropriate. Asterixis (tremor of wrist in dorsiflexion with forearm and fingers extended) may be seen in older children. It denotes postural lapse and consists of rapid flexion-extension movements akin to wing flapping of birds. Other neurological signs are hyper-reflexia, hypertonia, disruption of smooth pursuit of eye movements (SPEM) and occasionally nystagmus.

ETIOLOGY

Hepatic encephalopathy occurs as a result of ALF, chronic liver disease, or as a result of systemic disease (**Table 2**). The Pediatric Acute Liver Failure Study Group (PALFSG) has recently defined ALF as HE with international normalized ratio (INR) more than 1.5 (uncorrectable coagulopathy) or INR more than 2 without encephalopathy in the presence of biochemical liver injury and absence of pre-existing CLD.

NOMENCLATURE

After discarding the term *portosystemic encephalopathy*, the Hepatic Encephalopathy Consensus Group in 1998 standardized the nomenclature as shown in **Flow chart 1**. The differences between Type A and Type C HE are shown in **Table 3**. Definitions of different types of HE are given in **Table 4** and **Figures 2A to D**.

Table 2 Common causes of hepatic encephalopathy in children

Cause	Neonates and infants	Older children and adolescents
Acute liver failure	<ul style="list-style-type: none"> Galactosemia Tyrosinemia Hemochromatosis HLH Herpes simplex Hepatitis B Mitochondrial hepatopathy⁺ 	<ul style="list-style-type: none"> Hepatitis A, B, E Non-A-E (EBV, Parvo, Adenovirus) Drugs (paracetamol, ATT, valproate, halothane) Leptospirosis Reye syndrome[¥] Mushroom poisoning
Chronic liver disease	<ul style="list-style-type: none"> Decompensated biliary atresia Secondary biliary cirrhosis (choledochal cysts) Indian childhood cirrhosis PFIC (types I and II) GSD (type IV) Galactosemia Tyrosinemia Infantile sclerosing cholangitis 	<ul style="list-style-type: none"> Wilson disease Autoimmune liver disease Chronic hepatitis B or C Budd-Chiari syndrome Veno-occlusive diseases GSD (type III) PFIC (type III)
Systemic diseases	<ul style="list-style-type: none"> Malaria with complications Dengue shock syndrome Complicated typhoid Inborn errors of metabolism* Macrophage activation syndrome Connective tissue disorders (lupus hepatitis) Lymphoreticular malignancies 	

Abbreviations: HLH, hemophagocytic lymphohistiocytosis; PFIC, progressive familial intrahepatic cholestasis; GSD, glycogen storage disorders; ATT; anti-tubercular therapy.

⁺Mitochondrial hepatopathy refers to respiratory chain defects and some of the fatty acid oxidation defects presenting with acute liver failure.

^{*}Inborn errors of metabolism refers to mainly urea cycle defects, aminoacidopathies, organic acidemias and fatty acid oxidation defects presenting as acute intoxication and liver being a part of its multisystem involvement.

[¥]Age-specific (5–16 years): In classic or idiopathic variety often attributed to influenza, varicella or aspirin intake. In less than 5 years, (atypical) Reye-like syndrome is a manifestation of mitochondrial diseases, organic acidurias or urea cycle defects.

Table 1 Staging of hepatic encephalopathy: differences between infants/children and adults

Stage	Clinical	Reflexes	Neurological sign	EEG changes
0	None	Normal	None	Normal
I	<i>Infant/child:</i> Inconsolable crying, inattention to task; child is not acting like self to parents <i>Adult:</i> Confused, mood changes, altered sleep habits, forgetful	Normal or hyper-reflexic	Difficult or impossible to test adequately	Difficult or impossible to test adequately
II	<i>Infant/child:</i> Same as in stage I <i>Adult:</i> Drowsy, inappropriate behavior, decreased inhibitions	Normal	Tremor, apraxia, impaired handwriting	Normal or diffuse slowing to theta rhythm, triphasic waves
III	<i>Infant/child:</i> Same as in stage I <i>Adult:</i> Drowsy, inappropriate behavior, decreased inhibitions	Same as in stage I	Same as in stage I	Same as in stage I
IV	<i>Infant/child:</i> Somnolence, stupor, combativeness <i>Adult:</i> Stupor, obeys simple commands	Hyper-reflexic	Dysarthria, ataxia	Abnormal, generalized slowing triphasic waves
	<i>Infant/child:</i> Somnolence, stupor, combativeness <i>Adult:</i> Stupor, obeys simple commands	Hyper-reflexic Babinski sign +	Same as in stage I	Same as in stage I
	<i>Infant/child:</i> Comatose, arouses with painful stimuli (4a) or no response (4b) <i>Adult:</i> Comatose, arouses with painful stimuli (4a) or not	Absent	Rigidity	Abnormal, generalized slowing triphasic waves
	<i>Infant/child:</i> Comatose, arouses with painful stimuli (4a) or not	Absent	Decerebrate or decorticate	Abnormal
	<i>Infant/child:</i> Comatose, arouses with painful stimuli (4a) or not	Absent	Decerebrate or decorticate	Abnormal, very slow delta activity

Flow chart 1 Nomenclature and classification of hepatic encephalopathy (HE)
(World Congress of Gastroenterology: Hepatic Encephalopathy Consensus Group, 1998)

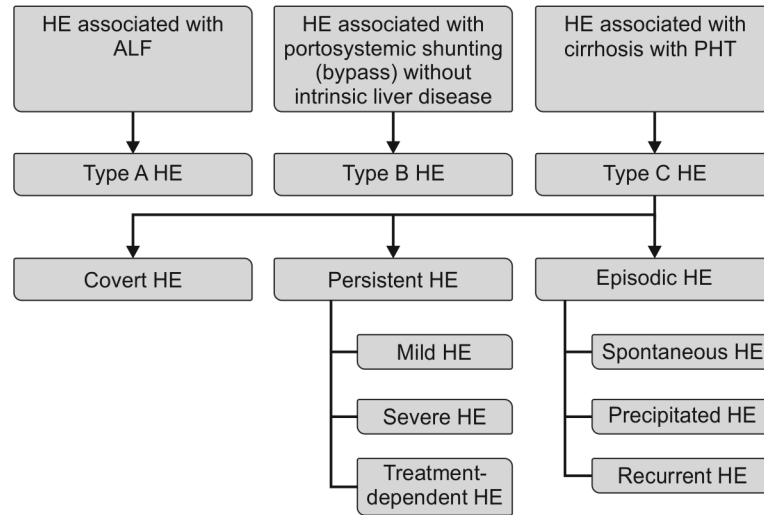


Table 3 Differences between Type A and Type C hepatic encephalopathy

Parameters	Type A	Type C
Pathology	Acute hepatocellular necrosis	Chronic hepatocellular injury Fibrosis, nodular regeneration Portosystemic shunting
Etiology	Acute liver failure	Chronic liver disease (cirrhosis)
Onset	Acute	Variable: insidious, acute
Precipitating factors	Uncommon	Common
Cerebral edema	High-grade edema	Low-grade edema
Nutritional status	Normal	Malnourished
Ascites	Absent	Usually present
Portosystemic shunts	Absent	Present
Treatment	Treat acute liver failure Consider liver transplantation	Treat precipitating cause with empirical therapy
Immediate survival	Low	High
Persistent neuropsychiatric sequelae after acute episode	No	Worsen cognitive functions

MINIMAL HEPATIC ENCEPHALOPATHY

Minimal hepatic encephalopathy (MHE) occurs classically in subjects with cirrhosis and is characterized by mild cognitive, psychomotor deficits and cerebral edema, affecting mainly attention, speed of information processing, motor abilities and coordination. MHE has also been recently reported in 35–50% of adult patients and 30% of children with extrahepatic portal venous obstruction (EHPVO) despite normal liver functions. Possible mechanism of MHE in EHPVO seems to be due to shunting of splanchnic blood directly into the systemic circulation bypassing

Table 4 Definitions of types of hepatic encephalopathy (HE)

Episodic HE	Encephalopathy of varying degree but lasting for short duration (Fig. 2A) <i>Precipitated HE</i> : Secondary to an identifiable precipitating factor <i>Spontaneous HE</i> : HE in the absence of a recognized precipitating factor
Recurrent HE	HE occurring \geq two times in 1 year with periods of symptom-free interval (Fig. 2B)
Persistent HE	Cognitive impairment at baseline lasting > 2 weeks secondary to liver disease (Fig. 2C). Affects social functioning
Minimal HE	Clinically normal mental status and normal neurologic examination but presence of cognitive defects in neuropsychometric tests
Overt HE	Clinically apparent encephalopathy of various degrees. Refer to Table 1 for classification
Covert HE	Clinically inapparent but revealed by psychometric tests. Encompasses minimal and subtle features of stage 1 HE (Fig. 2D).

hepatic detoxification. It is important to recognize MHE as it impairs the quality of life, which may improve with therapy. Other than ammonia, tumor necrosis factor alpha (TNF- α) has been shown to be a cause of MHE in children. MHE rarely occurs in EHPVO after surgical shunts.

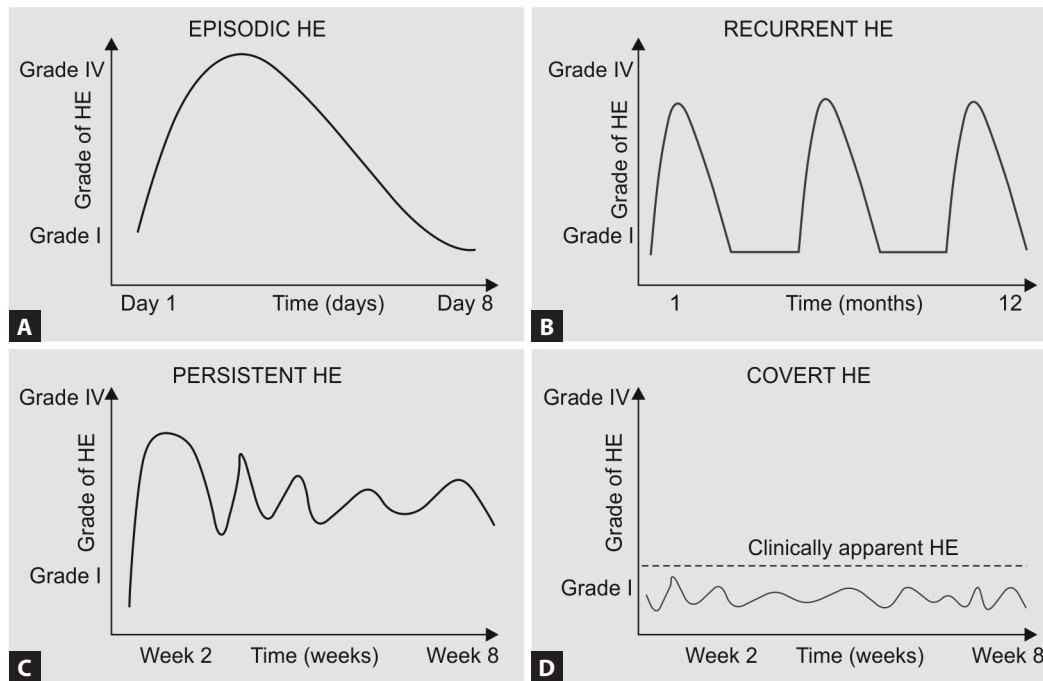
DIAGNOSTIC TESTS TO CONFIRM HEPATIC ENCEPHALOPATHY

Laboratory tests are not routinely recommended for confirmation of HE. Altered mental status in a patient with CLD or ALF created as HE unless proved otherwise.

Serum Ammonia

In ambiguous case scenarios, high serum ammonia (arterial/venous) helps to differentiate HE from other causes of encephalopathy.

- Blood should be collected from a stasis-free vein.
- Avoid clenching fist or application of tourniquet as ammonia may be released from skeletal muscle.
- Collect in a lithium or heparin vacutainer. Heparin inhibits release of ammonia from red cells.



Figures 2A to D Pattern of hepatic encephalopathy. The curved line depicts the pattern of hepatic encephalopathy. (A) Episodic HE; (B) Recurrent HE; (C) Persistent HE; (D) Covert HE

- Samples should be stored and transported in an ice bath within 20 minutes for assay.
- Normal ammonia levels vary in different age groups (**Table 5**).
A definite cut-off level for ammonia has not been established in HE. However, it has been shown in adult studies that ammonia levels less than 100 $\mu\text{mol/L}$ have overall better chances of survival. Levels less than 150 $\mu\text{mol/L}$ in severe HE have less chances of cerebral herniation. Levels more than 200 $\mu\text{mol/L}$ are invariably associated with cerebral herniation and poor outcome.

Psychometric Tests

These tests are difficult to perform in children. These are:

- *Paper and pencil tests*: Figure and number connection tests, Indian child intelligence test (6–12 years), Wechsler adult intelligence scale (> 13 years)
- Computerized psychometric tests (Clicker frequency test).

Electroencephalogram

Interpretation of electroencephalogram (EEG) changes (**Table 1**) in various stages of HE requires expertise by a pediatric neurologist.

Magnetic Resonance Imaging and Spectroscopy of Brain

Magnetic resonance imaging (MRI) changes in brain (high signal intensities in T1 weighted images or diffuse white matter signal intensities in fluid-attenuated inversion recovery [FLAIR] images) do not correlate with severity of HE.

Table 5 Normal ammonia levels in children

Age	Value ($\mu\text{mol/L}$)
< 30 days	21–95
1–12 months	18–74
1–14 years	17–68
>14 years	19–71

Other Tests

These include liver function tests (LFTs) including prothrombin time, metabolic profile (serum electrolytes, blood sugar, arterial blood gas analysis, kidney function tests), sepsis profile (complete blood count, blood and urine cultures, chest X-ray), ascitic fluid analysis and culture (for spontaneous bacterial peritonitis) and specific tests for underlying cause of ALF or CLD.

TREATMENT

A four-pronged treatment approach is advocated: (1) supportive care for altered mental status; (2) treating the underlying cause (disease-specific); (3) treating the precipitating cause; and (4) medical therapy.

Supportive Care

A child with hepatic encephalopathy should ideally be managed in an intensive care environment. The first step in management involves taking care of the airway, breathing and circulation as in all emergencies. Other steps in management are listed below:

- Fluid, electrolyte and blood sugar are management as per ALF protocol
- Nasogastric (NG) tube for feeding or oral drug delivery
- Nutrition through NG tube: 100–150 kcal/kg/day + 1 g/kg protein
- Positioning for prevention of decubitus ulcers
- Prophylactic acid suppressants (proton pump inhibitors) to prevent aspiration pneumonitis (gastroesophageal reflux due to NG tube) and prevent stress (Cushing's) ulcers and gastrointestinal (GI) bleed (which aggravates encephalopathy)
- Elective intubation (impending respiratory compromise) and prophylactic anticonvulsants in grade III or IV are controversial issues. Intravenous phenytoin 20 mg/kg loading followed by 5 mg/kg maintenance for impending seizures due to cerebral edema and nonconvulsive status epilepticus (not clinically apparent)
- Prophylactic antibiotics with adequate cover for Gram-positive and Gram-negative organisms

- 20% mannitol or 3% hypertonic saline in cerebral edema of ALF (not required in CLD).

Treatment of Precipitating Factors

Prompt identification and correction of precipitating factors (Table 6) may increase the recovery rates to 80–90%. Due to overlap or multiple precipitating factors, sometimes it is difficult to ascertain what actually reversed the encephalopathy.

- Aggressive treatment of sepsis with antimicrobials ± antifungals is warranted. Sepsis is capable of inducing encephalopathy on its own.
- GI bleed generates a large amount of ammonia through gut flora that precipitates hepatic encephalopathy. The absence of amino acid isoleucine from hemoglobin makes it more ammoniagenic than other forms of protein.
- Prevent constipation with laxatives (lactulose).
- Daily monitoring of fluid intake-urine output, serum electrolytes and metabolic parameters (arterial blood gas [ABG], creatinine) is recommended.
- Diuretics are preferably withheld or used with caution and vigilance.

Medical Therapy

Gut cleansing by catharsis (lactulose) or antimicrobials (e.g., rifaximin) is the mainstay of therapy for overt HE or for prophylaxis in cirrhotics. Other agents may have a role in minimal or mild HE (Table 7).

Lactulose

Lactulose is a nonabsorbable disaccharide. It lowers the colonic pH favoring formation of nonabsorbable ammonium ions, allows preferential growth of nonurease producing bacteria, reduces formation of potentially toxic short chain fatty acids, and has a cathartic action that flushes out bacteria from gut.

Though widely used as first-line therapy, there is lack of robust data to support use in overt HE. Many have argued that its efficacy is related to simple cathartic action that could be comparable to any other laxatives. Limited data is available to show that it is superior to placebo in covert or minimal HE. Dose is 1–2 mL/kg/dose in 3–4 doses orally or through NG tube. Goal is to have 2–3 acidic (pH < 6) loose stools/day. It can also be administered as enema, especially in the setting of constipation or ileus in HE. Side effects include: abdominal cramping, gaseous distension, diarrhea and flatulence.

Table 6 Factors precipitating or worsening hepatic encephalopathy (HE)

Precipitating factors	Confounding factors in HE (These are additional contributory factors that could worsen the underlying HE)
• Sepsis	• Status epilepticus or postictal state
• Gastrointestinal bleed	• Metabolic acidosis due to sepsis
• Dyselectrolytemia (hypokalemia, alkalosis, hyponatremia*)	• Sedatives (benzodiazepines) during procedure, seizures or combativeness
• Dietary protein overload	• Intracranial hemorrhage due to coagulopathy
• Dehydration	• Uremia (renal failure) due to sepsis or end-stage disease
• Diuretic use	
• Constipation or ileus	

*Hyponatremia may precipitate HE or aggravate cerebral edema. It is not clear whether hyponatremia is a true pathogenic factor or not.

Table 7 Medical therapy in hepatic encephalopathy

Therapy in overt HE	Prophylactic therapy in cirrhotics
<i>Lactulose</i> : First-line therapy	<i>Lactulose</i> : First-line therapy
<i>Rifaximin</i> : Second-line add on therapy	<i>Rifaximin</i> : Second-line add on therapy (lactulose failure)
<i>Sodium benzoate</i> : adjunct in refractory HE or first-line in urea cycle defects (UCD)	LOLA (L-ornithine L-aspartate): adjunct therapy
<i>Neomycin</i> : abandoned	<i>Sodium benzoate</i> : Adjunct therapy
intravenous flumazenil (short-lasting therapy in adults)	<i>Diet</i> : Vegetable protein-based diet Branched chain amino acid supplement
<i>Protein intake</i> : Protein restriction is no longer recommended except transiently to approximately 0.5 mg/kg during the phase of acute encephalopathy. After recovery, daily protein intake should be 1.2–1.5 g/kg/day for ensuring growth and muscle mass. Small meals or liquid nutritional supplements evenly distributed throughout the day and a late night snack should be offered to prevent hypoglycemia.	
Vegetable or dairy-based protein diet is preferred as it contains high ornithine and arginine that facilitate ammonia disposal and low sulfated amino acids (methionine and cysteine) that are precursors of indoles and mercaptans (precipitants of HE). In addition, the fiber from the plant based diet also enhances ammonia disposal by faster intestinal transit, lowering colonic pH and allowing proliferation of favorable microbiota. Short chain fatty acids released from undigested fiber in colon provide additional calories to the patient. Hence, vegetable-based protein diet offers higher calorie: nitrogen ratio as compared to animal protein. Oral BCAA serves as supplement to the existing dietary protein or to those who are intolerant to the same.	
Primary prophylaxis for prevention of episodes of overt HE is not required, except in patients with cirrhosis with a known high-risk to develop HE.	

Rifaximin

This is a broad-spectrum antibiotic with poor oral bioavailability. It is solubilized by bile salts with maximum action on small bowel bacteria. Once bile salts are absorbed into enterohepatic circulation, rifaximin becomes less active and, therefore, action on colonic bacteria is minimal. Though widely used, studies have not yet shown its superiority over other agents in acute HE. However, it prevents recurrent HE episodes in cirrhotics, especially in those with lactulose treatment failure in adult. Dose schedule is not available for children; in adults it is given as 550 mg twice daily. Combination of rifaximin and lactulose has shown to be superior to lactulose alone in cirrhotic adults with overt HE.

Neomycin and Other Antibiotics

Recent studies have shown no benefit over lactulose or placebo. It inhibits anaerobes and also intestinal mucosal glutaminase activity (reduced ammonia in portal vein). It has been abandoned due to ototoxicity and nephrotoxicity. Metronidazole and vancomycin have also been tried in limited clinical trials with some success in overt HE.

L-Ornithine L-Aspartate

Activates carbamyl phosphate synthetase and ornithine carbamyl-transferase in urea cycle to stimulate glutamine synthesis and detoxify ammonia. L-Ornithine L-Aspartate (LOLA) is administered intravenously 6g three times a day in adults. Experience in children is limited. It is used in mild HE or as prophylaxis in HE, especially those with transjugular intrahepatic portosystemic shunts (TIPS). Oral supplementation of LOLA is ineffective

Branched Chain Amino Acids

This supplement has been used in an attempt to restore the altered BCAA/AAA ratio in the brain to produce *true neurotransmitters*. It is used in early encephalopathy and for prophylaxis in chronic encephalopathy due to hepatic cirrhosis. The dose varies between 0.24 mg/kg/day and 0.45 mg/kg/day once or in two divided doses. An updated meta-analysis of eight randomized, controlled trials (RCTs) indicated that oral BCAA-enriched formulations improve the manifestations of episodic HE whether overt or minimal. There is no effect of IV BCAA on the episodic bout of HE.

Molecular Adsorbent Recirculating System

Just like hemodialysis, molecular adsorbent recirculating system (MARS) *cleanses* blood via an albumin circuit and bicarbonate dialyzer. MARS ameliorates hepatic encephalopathy and other clinical manifestations of ALF by removing both water-soluble and protein-bound toxins. It is a bridge to liver transplantation and is highly expensive.

Liver Transplantation

It should be considered when medical therapy fails or other complications ensue. Recurrent intractable overt encephalopathy in a patient with liver failure is an indication for liver transplant.

MITOCHONDRIAL HEPATOPATHIES

Mitochondria, the *powerhouse* of a cell, are the site for beta oxidation (aerobic pathway) that generates 38 adenosine triphosphate (ATP) through the Krebs's cycle and respiratory chain. Various mutations in mitochondrial deoxyribonucleic acid (DNA) result in enzyme deficiencies that fail to generate energy. Liver, brain and heart (high dependency sites) are most affected as 80% of their functions depend on beta-oxidation. Conventionally, mitochondrial hepatopathies (MH) comprise of fatty acid oxidation and respiratory chain disorders as their presentation overlaps. Defects of fatty acid oxidation have been discussed in detail in Section 3.

Settings to Suspect to Mitochondrial Hepatopathies

- Recurrent symptoms (acidosis, ketosis, high lactate);
- Rapid deterioration with minor illness upper respiratory tract infections (URI) with quick recovery after intravenous (IV) fluids;
- Developmental delay in a child with acute encephalopathy;
- Multisystem involvement (neurodevelopmental delay, cardiomyopathy and peripheral myopathy);
- Reye like illness (details later);
- Unexplained liver failure (toddlers) with negative viral markers; and
- Fatty liver on ultrasound, steatosis on liver biopsy with or without raised transaminases with nonspecific symptoms or multisystem involvement.

Family history of consanguinity (28%), sibling deaths (43%) or affected sibs contribute to the disease. Maternal history of acute fatty liver of pregnancy or HELLP (hemolysis, elevated liver enzymes, low platelet and liver failure) syndrome could indicate very long chain or long chain fatty acid oxidation disorder (FAOD) in fetus. Among the FAODs, medium chain fatty acid defects may present with recurrent encephalopathy but have better prognosis if symptom onset is more than 6 years of age. Long chain and very long chain diseases have worse outcome and a large proportion have multisystemic disease with liver failure. Respiratory chain defects invariably have liver failure.

Urea Cycle Defects

Urea cycle defects (UCDs) result from enzymes deficiencies at various levels of urea cycle pathway leading to severe

hyperammonemia. Severe deficiency presents in the first 2 weeks of life with lethargy, coma and seizures. Moderate deficiency presents in childhood with recurrent or intractable encephalopathy especially after high protein diet. Jaundice and liver failure are usually not associated with urea cycle defects. These disorders are discussed in detail in Section 3 on Metabolic Disorders.

Laboratory Diagnosis

A brief approach to work-up for MH and urea cycle disorders is mentioned in **Flow chart 2**. Creatinine phosphokinase may be elevated in associated myopathies of MH. Certain precautions are important before linking abnormal tests to basic metabolic liver disease. Lactate levels may be elevated in intercurrent sepsis and, therefore, the test should be repeated to document elevated levels in the recovery phase of illness to conclude hyperlactatemia. Urine ketone bodies must be repeated more than once to give a negative label. Serum ammonia levels are 80–200 $\mu\text{mol/L}$ in FAOD and 150–300 $\mu\text{mol/L}$ in UCD. The definite diagnosis of inborn errors of metabolism are done by gas chromatography and tandem mass spectrometry with quantitative assay of the deficient enzyme in blood and toxic metabolites in urine. For MH, liver and muscle biopsy may help in quantifying respiratory chain enzymes. For details, refer to Section 3 on Metabolic Disorders.

Treatment

Acute and long-term treatment of MH and UCD is outlined in **Table 8**. MH is usually treated with supportive management, carnitine and other supplements that have no proven role. UCD is treated with ammonia-lowering agents such as sodium benzoate and phenylacetate and other drugs mentioned in **Flow chart 3**.

Carnitine

The role of carnitine is controversial as no proven benefit exists. It is life-saving in patients who have primary carnitine deficiency and valproate toxicity. Carnitine is usually supplemented in FAOD due to a relative secondary carnitine deficiency in the mitochondria to remove toxic acyl-CoA intermediates. Risk of arrhythmias in long chain FAOD has been noted with carnitine supplementation.

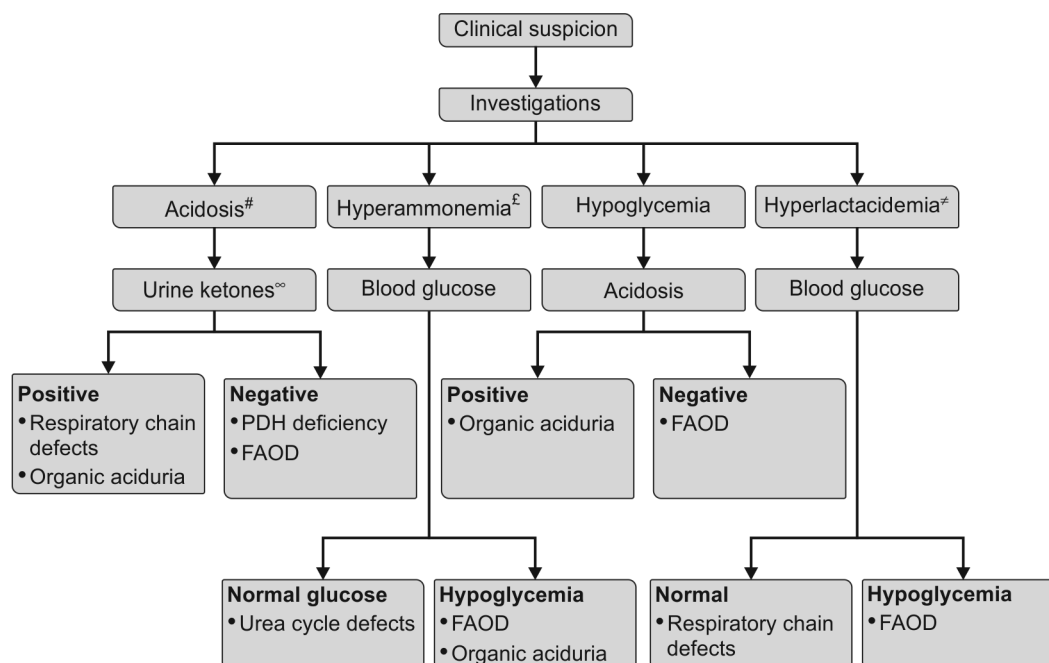
Sodium Benzoate and Phenylacetate

Sodium benzoate and phenylacetate are used in acute HE, particularly in UCD and occasionally in FAOD. Glycine combines with benzoate to form hippurate. Glutamine combines with phenylacetate to form phenylacetylglutamine. These by-products are effectively excreted in urine, thereby reducing the ammonia load that is not being metabolized in a defective urea cycle. Additionally, sodium benzoate has not been shown to be superior to lactulose in randomized trials in adult cirrhotics. It may be used as an adjunct in refractory HE. Excessive sodium precludes its use in those with pre-existing ascites or renal dysfunction.

REYE SYNDROME

Reye syndrome (RS) is a secondary cause of MH. The British Pediatric Surveillance Unit defines RS as an unexplained, noninflammatory encephalopathy in those less than 16 years of age, associated with a serum aspartate or alanine aminotransferases, or plasma ammonia more than three times the normal limit, or hepatic fatty infiltration that is microvesicular in appearance and panlobular in distribution.

Reye syndrome is a biphasic illness. A viral prodrome with infection of the upper respiratory tract with influenza virus (90%) or chickenpox (5–7%) precedes encephalopathy. It is followed several days later by an abrupt onset of encephalopathy heralded as profuse, effortless vomiting. The rate and degree of neurological decline vary. Raised intracranial pressure from brain swelling

Flow chart 2 Approach in mitochondrial hepatopathy, organic aciduria and urea cycle defect

[#] Arterial blood gas to look for pH, bicarbonate and anion gap [sodium – (chloride + bicarbonate), normal 12–18, abnormal > 20], [£] Arterial sample, [±] Arterial sample, [∞] At the time of blood sugar estimation, Abbreviations: PDH, pyruvate dehydrogenase; FAOD, fatty acid oxidation defect.

Table 8 Treatment of mitochondrial hepatopathy and urea cycle defects

Acute	Long-term	Prevention
10–12.5% dextrose infusion	Carnitine 50–100 mg/kg/d	Avoidance of fasting
Bicarbonate, K+ supplementation	Coenzyme Q ₁₀ 3–5 mg/kg/day	Infancy: Feeding every 3–4 hourly or continuous nasogastric feeding
Carnitine (100 mg/kg) intravenous till oral acceptability	Vitamin E 25 IU/kg/day	Older children: Corn starch therapy (1–2 gm/kg/dose) every 4–6 hourly
Sodium benzoate and phenylacetate (100–250 mg/kg till ammonia levels normalize)	Other supplements: creatine and dichloroacetate	Medium chain triglyceride [#] (MCT) supplementation as 20% of caloric intake

[#]MCT does not require carnitine cycle to cross mitochondrial membrane.

may result in death or neurological injury. Aspirin use is strongly associated as a causal role in the illness. Aspirin metabolites inhibit beta oxidation of long chain fatty acids. Precipitation of RS by use of antiemetics is controversial. *Classical* RS presents with the earlier features between 5 years and 15 years. In children less than 5 years of age, FAOD and UCD mimic RS (Reye-like illness). It is also believed that RS in childhood may be one of the first clues of an inborn error presenting later in adulthood. Declining use of aspirin is also associated with declining incidence of RS. Others believe that decline is attributed to increased detection of inborn errors from neonatal screening programs and early management of the same.

As the incidence of RS is dramatically decreasing and newer enzymatic defects are being discovered, it has become imperative to search for inherited metabolic diseases in all age groups (especially < 5 years) with RS. The key laboratory feature that distinguishes RS

from other encephalopathies is near normal bilirubin (< 5 mg/dL) in the presence of very high enzymes, elevated prothrombin time and hyperammonemia. Manifestations and management are same as that of ALF.

CONGENITAL PORTOSYSTEMIC SHUNTS

This is a rare developmental anomaly in children where there is lack of complete involution of embryonic or fetal communications between veins of portal system and inferior vena cava. The diversion of blood flow may be partial or total. Communications can be single or multiple. Location can be extrahepatic (Abernathy malformation and congenital absence of portal vein) or intrahepatic. The condition may be associated with other malformations including biliary atresia, polysplenia, gut malformations and congenital heart diseases.

Diagnosis

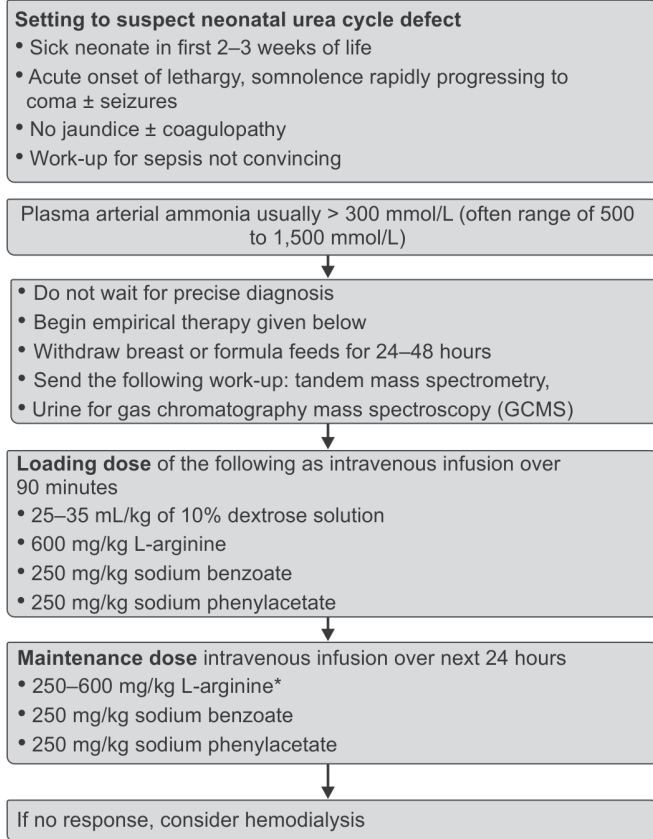
Encephalopathy in congenital portosystemic shunts (CPS) is usually recurrent or intractable. Diagnosis should be suspected in children who have lethargy and confusion especially after meals; those with mental retardation with seizures, learning difficulties, behavioral abnormalities and hyperactivity. Other settings to suspect are enlisted as follows:

- Neonatal cholestasis with recurrent hypoglycemia but non-enlarged liver;
- Early onset pulmonary hypertension (mean: 5 years);
- Hepatopulmonary syndrome without overt features of cirrhosis (mean: 4 years); and
- Incidental radiological finding: small liver (45–65% of estimated volume for age) and absence of portal vein.

Management

Hyperammonemia, slow wave EEG changes and globus pallidus hyperintensities on MRI brain are often seen. Doppler ultrasound

Flow chart 3 Management algorithm for acute neonatal hyperammonemic crisis



- * If precise diagnosis is made by this time, then
- 250 mg/kg of L-arginine for carbamyl phosphate synthetase (CPS) I and ornithine transcarbamylase (OTC) deficiency
 - 600 mg/kg of L-arginine for citrullinemia and argininosuccinic aciduria
 - For argininosuccinic aciduria, arginine therapy alone may suffice.

and portovenography are the key imaging modalities. Long-term complications include liver hemangioma, adenoma or focal nodular hyperplasia (mean: 8 years) with propensity to become malignant. With exception of neonatal cholestasis where the

shunts may resolve spontaneously, the rest persist and require radiological or surgical closure. Early closure is advocated to prevent pulmonary and neurological complications. Liver transplantation is usually not required.

IN A NUTSHELL

1. Hepatic encephalopathy refers to a variety of reversible neurologic abnormalities seen in patients with cirrhosis and liver failure. Manifestations arise because of three factors: portosystemic shunting, alterations in the blood-brain barrier, and the interactions of toxic metabolites with the central nervous system (CNS).
2. Ammonia is the principal toxin responsible for encephalopathy. Hypokalemia, metabolic alkalosis and sepsis contribute to brain dysfunction.
3. Hepatic encephalopathy may occur secondary to acute liver failure, chronic liver disease, mitochondrial defects, or systemic disorders.
4. Minimal hepatic encephalopathy (MHE) occurs classically in subjects with cirrhosis and is characterized by mild cognitive, psychomotor deficits and cerebral edema, affecting mainly attention, speed of information processing, motor abilities and coordination.
5. A four-pronged treatment approach is advocated: supportive care for altered mental status, treating the underlying cause (disease-specific), treating the precipitating cause and medical therapy.

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Chapter 37.10

Acute Liver Failure

Anupam Sibal, Vidyut Bhatia, Akshay Kapoor

Acute liver failure (ALF) is a devastating illness with a high mortality rate. It occurs as a consequence of rapid death or injury to a majority of hepatocytes, thereby compromising liver function to a significant extent. Acute on chronic liver failure refers to an acute decompensation of pre-existing liver disease secondary to an identified or unidentified liver disorder. The Pediatric Gastroenterology Chapter of the Indian Academy of Pediatrics (IAP) has published guidelines for the management of ALF in 2013. The management of ALF described in this chapter is largely based on those guidelines.

DEFINITION

The Pediatric Gastroenterology Chapter of IAP defines acute liver failure in the presence of (1) evidence of liver dysfunction within 8 weeks of onset of symptoms (neonates may have only deranged liver functions without overt symptoms); (2) uncorrectable (6–8 hours after administration of one dose of parenteral vitamin K) coagulopathy with international normalized ratio (INR) more than 1.5 in patients with hepatic encephalopathy (HE) or INR more than 2.0 in patients without encephalopathy; and (3) no evidence of chronic liver disease either at presentation or in the past.

INITIAL ASSESSMENT

The history taken at the first contact should include details about the onset of jaundice, changes in the sensorium like excessive sleepiness, excessive crying, altered sleep and wake cycle, evidence of altered coagulation in the form of bleeding from the nose, vomiting of blood, black-colored stools or ecchymosis. History of blood transfusions in the past, onset in relation to recent ingestion of drugs, like acetaminophen, valproate or drugs used for tuberculosis, are also important. Similar presentations in the past would point out to a chronic underlying etiology. History should also include asking for consanguinity or family history suggestive of Wilson disease, early infantile death, viral hepatitis and autoimmune conditions.

Physical examination should include the assessment of growth and search for signs of chronic liver disease. It is important to evaluate the nutritional status of the child. The abdominal examination should include measurement of liver span, the size of the spleen and presence of fluid in the abdomen. A comprehensive systemic examination should be done keeping in mind that ALF has a multisystem involvement.

Management should commence immediately with concurrent etiological work-up.

ETIOLOGY

Few studies have looked into the etiology of ALF in India. There are no prevalence- or population-based studies available. Studies from referral centers reveal that infectious hepatitis (secondary to viral hepatitis type A, E) is the most important cause of ALF (Table 1). Studies from the West, however, show a different picture. In the largest multicentric pediatric study on ALF in 348 children, the etiology included acute acetaminophen toxicity (14%), metabolic disease (10%), autoimmune liver disease (6%), nonacetaminophen drug-related hepatotoxicity (5%), infections (6%) and other diagnosed conditions (10%). The largest proportion of cases (49%) was indeterminate. As a subgroup, in infants and

newborns, inherited metabolic disorders are responsible for the majority of cases.

WORK-UP

The initial investigations should focus on establishing the cause, as also performing a baseline evaluation of the patient's biochemical status (Table 2). It is important to stratify investigations depending on the demographic status of the child. Not all investigations for establishing etiology are needed in every child. For example, a child of 2 years of age should not be investigated for Wilson disease because it is very unlikely to present at this age. Similarly, it is very unlikely that an 11-year-old is likely to suffer from an inherited multisystem disorder of metabolism.

MANAGEMENT

Acute liver failure has a progressively evolving unpredictable course. Raised intracranial pressure, infections and multiorgan failure are the major causes of mortality in children with ALF. Efforts should be made to ameliorate these conditions while waiting for the native liver function to recover or for a liver transplantation. Most management recommendations are based on expert group consensus, or extrapolated from case series or adult studies.

Immediate Measures

The child should be nursed in a calm and quiet environment in an intensive care setting. A central line should be placed to

Table 1 Indian studies on children with acute liver failure

Year of study	Location	n	Contribution by infectious hepatitis (%)
1996	New Delhi	40	75%
1999	Pune	36	61.1%
2002	Chandigarh	67	94%
2004	New Delhi	32	62.5%
2005	Vellore	22	Not clear
2007	Kolkata	45	66.6%
2012	Delhi	43	77%

Table 2 Investigations in infants and children with acute liver failure

Baseline investigations
<ul style="list-style-type: none"> Complete hemogram; serum electrolytes; blood sugar; arterial blood gas Liver function tests; kidney function tests; cholesterol; prothrombin time Blood ammonia, lactate Ultrasound abdomen
Investigations for establishing etiology
<ul style="list-style-type: none"> Viral markers; HAV IgM; HEV IgM; HBcIgM; HBsAg; Anti-HCV Autoimmune markers: ANA/SMA/LKM/SLA Serum ceruloplasmin; eye examination (KF ring); 24-hour urinary copper excretion
Special investigations for neonates and infants
<ul style="list-style-type: none"> Urinary succinylacetone GALT assay Alfa-fetoprotein Serum ferritin

Abbreviations: HAV, hepatitis A virus; IgM, immunoglobulin M; HEV, hepatitis E virus; HBcIgM, hepatitis B core antigen; HCV, hepatitis C virus; SLA, soluble liver antigen; SMA, smooth muscle antibody; ANA, antinuclear antibody; LKM, liver-kidney microsomal antibodies; GALT, galactose-1-phosphate uridyl transferase.

assess central venous pressure, administer intravenous (IV) fluids, medications and blood products. Blood samples can also be collected as the line obviates the need for repeatedly pricking the patient. Intravenous fluids are targeted towards meeting daily requirement and insensible losses. The glucose infusion rate should be 6–8 mg/kg/min titrated to maintain a glucose level between 150 mg/dL and 200 mg/dL. The composition of maintenance fluids can be tailored to the electrolyte, sugar and renal status of the patient. Inotropes like dopamine and dobutamine can be used if the patient is hypotensive. Strict fluid charting should be maintained and the fluids given as part of preparing solutions for antibiotics should be accounted for. A nasogastric tube should be inserted for feeding/drainage and a urinary catheter for output measurement. Care of bowel, back, bladder, skin, eyes should be provided. Monitoring of clinical and biochemical parameters should be done frequently until the patient becomes stable (**Table 3**).

Mechanical ventilation of patients in grade III or IV encephalopathy or those with significant hypoxemia is necessary. Sedation in intubated patients may be carried out using midazolam or propofol. For painful or invasive procedures, a short acting agent like propofol is preferred. Medications having the propensity to alter the level of consciousness should be avoided.

Metabolic, Electrolyte and Acid-base Disturbances

An important aspect of the management of ALF is to manage the associated metabolic complications which occur frequently. The most commonly seen disturbances are both low and high levels of sodium, calcium, potassium, low phosphate levels and acid-base disturbances.

Management of Intracranial Hypertension

The most dreaded complication of ALF is the development of intracranial hypertension (ICH). In patients who have grade III–IV hepatic encephalopathy, 70–80% patients can develop ICH. It is also the most common cause of death in these children. In addition, development of raised ICH could preclude the feasibility of liver transplant as the chances of irreversible neurological damage are very high. Head end elevation to 30° and elective endotracheal intubation are recommended. Prophylactic administration of 3% saline is recommended in patients with severe encephalopathy. The target sodium should be at 145–155 mmol/L. 20% mannitol solution can be given as a bolus in a dose of 0.5 g/kg if there is an acute rise of intracranial pressure. Care should be taken to avoid increasing the serum osmolality to more than 320 mOsm/L.

Table 3 Monitoring of clinical and biochemical parameters

• Continuous saturation monitoring
• Continuous monitoring of vital signs
• 6 hourly neurological assessment
• 8 hourly electrolyte, sugar and arterial blood gases
• 12 hourly coagulation studies
• Daily measurements of liver span
• Daily full blood counts, LFT and KFT
• Daily weight (using special weighing scales when the patient cannot be mobilized)
• Daily prescription review
• Twice weekly calcium and phosphate
• Surveillance blood and urine cultures

Abbreviations: LFT, liver function test; KFT, kidney function test.

Management of Coagulopathy and Hemorrhage

Coagulopathy is an inevitable accompaniment of ALF. A single dose of IV vitamin K should be given to correct any reversible coagulopathy. Care should be taken to use vitamin K₁, as routinely available vitamin K preparation can cause hemolysis in G6PD-deficient individuals. Correction of coagulopathy with fresh frozen plasma is not recommended routinely as it interferes in the assessment of the progression of the disease and suitability for a liver transplant. It should only be given when there is active bleeding or when an invasive procedure is planned or if coagulopathy is very severe (INR > 7). Platelet count and function are depressed on account of ALF and contribute to increased coagulopathy. A low platelet count should be corrected if the platelet count falls below $20 \times 10^9/L$ or with active hemorrhage or before any planned invasive procedure. The most common site of bleeding is from the gastrointestinal tract; hence, prophylactic administration of proton pump inhibitors is routinely recommended.

Sepsis

Bacterial infection is one of the leading causes of mortality in patients with ALF. The most common organisms isolated are Gram-positive cocci (staphylococci, streptococci) and enteric Gram-negative bacilli. Fungal infections, especially *Candida* spp., may be present in up to one-third of patients with ALF. Empirical antibiotics should be avoided but are recommended in the IAP guidelines in the following situations: surveillance cultures reveal significant isolates, progression of, or advanced stage (III/IV) hepatic encephalopathy, refractory hypotension, renal failure, presence of systemic inflammatory response syndrome components (temperature > 38°C or < 36°C, white blood cells [WBC] count > 12,000 or < 4,000/mm³, tachycardia) and listing for liver transplant since infection often results in delisting and immunosuppression postliver transplantation is imminent. Broad-spectrum coverage with a third-generation cephalosporin, vancomycin/teicoplanin, and fluconazole are recommended.

Feeding

Oral or nasogastric feeding is usually well-tolerated and should be started as early as possible. Enteral route of feeding, being more physiologic, is preferred. Vegetable source of protein is preferred. The recommended nutritional intake in children with liver failure is summarized in **Table 4**.

Specific Management

Specific therapy should be administered if the underlying cause of ALF has been identified (**Table 5**).

Role of N-Acetyl Cysteine and L-Ornithine L-Aspartate

The evidence for use of N-acetyl cysteine (NAC) in causes other than acetaminophen poisoning is increasingly being recognized. NAC can be used in the dose of 100 mg/kg/day. Although its role has been questioned in a recently published multicentric study, it continues to be used at most centers. A randomized controlled trial on the benefits of L-ornithine L-aspartate (LOLA) failed to demonstrate any benefit in terms of mortality or lowering of ammonia in patients with ALF.

Liver Transplantation

Liver transplantation remains the only definite therapy for ALF in children. It has transformed the management of ALF. Several prognostic scoring systems have been devised to predict mortality and to identify those requiring early liver transplant. These include King's College Hospital (KCH) criteria, pediatric end-stage liver disease (PELD) score, APACHE II and Clichy criteria. The IAP consensus statement recommends using an INR more than

Table 4 Recommended dietary intakes for children with acute and acute on chronic liver failure

Component	Recommended intake	Comments
Calories	150% of recommended allowance	Children with long-standing liver disease already suffer from varying degrees of malnutrition, therefore, need extra calories
Carbohydrates	15–20 g/kg/day	
Fat	8 g/kg/day with 50% as medium chain triglycerides	
Protein (non-encephalopathic)	2–3 g/kg/day	For promoting growth and to maintain positive nitrogen balance. Vegetable and dairy product based
Protein (encephalopathic)	Low-grade (I–II) 1–2 g/kg/day High-grade (III–IV) 0.5–1 g/kg/day	Further protein restriction can exacerbate HE by causing breakdown of endogenous protein

Abbreviation: HE, hepatic encephalopathy.

Table 5 Etiology-specific management of underlying acute liver failure (ALF)

Etiology	Management
Herpes simplex virus	Acyclovir
Acetaminophen poisoning	NAC oral: 140 mg/kg loading dose followed by 17 doses of 70 mg/kg every four hours for a total of 1,330 mg/kg over 72 hours NAC IV intermittent: 140 mg/kg loading dose followed by 12 maintenance doses of 70 mg/kg every 4 hours NAC IV infusion: Loading dose 150 mg/kg infused over 15 minutes, followed by 50 mg/kg infused over 4 hours and then 100 mg/kg infused over 16 hours
Acute severe autoimmune hepatitis	Methyl prednisolone
Galactosemia	Galactose and lactose-free diets
Fructosemia	Fructose-free diets, avoiding fructose and sorbitol infusions
Tyrosinemia	Nitisinone, phenylalanine and tyrosine-free diets
Bile acid synthesis defects	Primary bile acid therapy
Neonatal hemochromatosis	Intravenous immunoglobulin, exchange transfusion

Abbreviation: NAC, N-acetyl cysteine.

4 or factor V concentration of less than 25% as the best available criteria for listing for liver transplant. Contraindications for liver transplantation are active uncontrollable and untreatable sepsis, severe cardiopulmonary disease, multiorgan failure, mitochondrial disease, and hepatic encephalopathy stage IV with severe neurological impairment.

Artificial Detoxification Systems

In ALF, since most of the toxins are albumin-bound and are not filterable using conventional dialysis, different albumin dialysis systems have been developed using albumin as the scavenging

molecule. Artificial support systems can be broadly grouped into the biological (bioartificial liver) and nonbiological (molecular adsorbent recirculation system and prometheus systems) categories. None of these systems have demonstrated any survival benefit in the pediatric population as compared to the conventional management of ALF.

PROGNOSIS AND OUTCOME

In more than 50% of children with ALF, there is poor survival unless liver transplant is offered at the appropriate time. Prognostic factors predicting outcome in acute liver failure include elevated serum bilirubin and prothrombin time, young age of the child, high arterial ammonia and high WBC count, low alanine aminotransferase and presence of encephalopathy. The outcome is better with hepatitis A, acetaminophen overdose and ischemia (approximately 60% spontaneous survival) and poor with drug-induced ALF (non-acetaminophen), hepatitis B, and indeterminate cases (25% spontaneous survival).

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IN A NUTSHELL

1. The Pediatric Gastroenterology Chapter of IAP defines acute liver failure (ALF) in presence of (1) evidence of liver dysfunction within 8 weeks of onset of symptoms, (2) uncorrectable coagulopathy; and (3) no evidence of chronic liver disease either at presentation or in the past.
2. Infectious hepatitis (secondary to viral hepatitis type A, E) is the most important cause of acute liver failure in India.
3. Raised intracranial pressure, infections and multiorgan failure are the major causes of mortality in children with ALF.
4. Broad-spectrum coverage with a third-generation cephalosporin, vancomycin/teicoplanin, and fluconazole are recommended.
5. Liver transplantation remains the only definite therapy for acute liver failure in children.

Chapter 37.11

Liver Tumors

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Primary liver tumors are rare in children and the most common neoplasm involving the liver is usually a metastatic disease either from neuroblastoma, Wilms tumor or lymphoma. The reported incidence of liver tumor in children is around 0.5–2.5 per million population. Two-thirds of primary liver tumors are malignant with hepatocyte-derived tumors being more common than the mesenchymal tumors. Hemangiomas and hamartomas are the most common benign liver tumors, while hepatoblastoma is the most common primary malignant liver tumor in children. Majority of liver tumors per se do not cause cholestasis or synthetic dysfunction. **Table 1** enlists the various tumors of the liver.

HEMANGIOENDOTHELIOMA

Hemangioendotheliomas are the most common benign liver tumors and represent around 30% of all hepatic tumors in children. The incidence might be much higher as small hemangioendothelioma remains asymptomatic and involutes spontaneously. They commonly present within first 6 months of life and more than 90% are diagnosed before 6 years of age. Hemangioendothelioma has a female preponderance with 2–4.3

times more common than males. They are derived from the vascular endothelium and the natural history could be divided into three phases:

1. Phase of rapid growth from birth to 12 months, characterized by rapidly dividing endothelial cells, myeloid cells and pericytes.
2. Involuting phase lasting for 5–7 years, where apoptosis predominates.
3. Involved phase where the original lesion is replaced by fibrofatty tissue.

Clinical Presentation

Hemangioendotheliomas usually present with an abdominal mass or with heart failure. Multiple cutaneous hemangiomas should raise the possibility of visceral hemangiomas. Associated abnormalities include atrial septal defect, patent ductus arteriosus, myelomeningocele, renal agenesis and absent common bile duct. A good proportion of hemangioendotheliomas present with cardiac failure due to large arteriovenous or portovenous shunts. Platelet sequestration and consumptive coagulopathy can occur (Kasabach-Merritt syndrome) and sometimes there is an associated hypothyroidism due to overproduction of type 3 iodothyronine deiodinase. Large tumors can cause inferior vena cava compression, abdominal compartment syndrome and respiratory compromise.

Diagnosis

Full blood count and liver function test would be usually normal. In case of Kasabach-Merritt syndrome with disseminated intravascular coagulation, there might be low platelets and coagulopathy. *Ultrasonography* of the liver might reveal a predominantly hypoechoic lesion with well-defined margins and a Doppler might show flow of blood in the lesion. *Contrast computed tomography* (CT) scan would show isodense or hypodense lesions with uniform or centripetal contrast-enhanced lesion. *CT angiography* would reveal flow voids, enlarged hepatic arteries or veins or aortic tapering distal to the origin of hepatic artery indicating shunting. On *magnetic resonance imaging* (MRI), hemangioendotheliomas appear as low signal lesions on T1 weighted images as against high signal lesions on T2 weighted images. Because of lack of Kupffer cells, ^{99m}Tc sulfur colloid *scintigraphy* shows hemangioendothelioma as a cold spot.

Biopsy is usually not required but in case of diagnostic dilemma, an open biopsy is preferred than a percutaneous biopsy due to the vascular nature of the tumor. Biopsy might show two distinguished histological types. Type 1 lesions consist of small vascular channels lined by flat or round endothelial cells displacing the portal tract, with no features of infiltration or mitosis. Type 2 lesions consist of tortuous vascular channels with pleomorphic endothelial cells proliferating into the adjacent hepatic tissue, which might mimic angiosarcoma.

Treatment

Most hemangiomas regress spontaneously. Treatment is indicated only if there are associated complications like high output states such as tachycardia/cardiac failure or pressure effect due to the size of the tumor. Supportive treatment with inotropes and diuretics is warranted in cardiac failure. Definitive treatment includes steroids (prednisolone for 6 weeks), vincristine, cyclophosphamide or daily subcutaneous interferon alpha-2a therapy. Symptomatic hemangioendothelioma that has failed to resolve with medical managements may be treated surgically. Debulking, hepatic artery ligation and radiological interventions like transcatheter endovascular tumor chemoembolization could be tried. Liver transplantation is an option for difficult to treat tumors.

Table 1 Classification of liver tumors

Benign solid tumors	Malignant tumors
<i>Primary liver tumors</i>	
a. Epithelial tumors:	• Hepatoblastoma
• Hepatocellular adenoma	• Hepatocellular carcinoma
• Bile duct adenoma	• Undifferentiated sarcoma
• Biliary cystadenoma	• Biliary rhabdomyosarcoma
• Biliary papillomatosis	• Angiosarcoma
• Peribiliary gland adenoma	• Epitheloid
b. Mesenchymal tumors:	hemangioendothelioma
• Hemangioma	• Rhabdoid tumors
• Infantile hemangioendothelioma	
• Fibroma	
• Angiomyolipoma	
• Lipoma	
• Lymphangioma	
• Mesenchymal hamartoma	
c. Mixed tumors:	
• Teratoma	
d. Tumor-like lesions:	
• Focal nodular hyperplasia	
• Nodular regenerative hyperplasia	
• Microhamartoma (von Meyerburg complex)	
• Inflammatory pseudotumor	
• Focal fatty change	
• Pseudolipoma	
• Microregenerative nodule	
<i>Metastatic liver tumors</i>	
• Neuroblastoma	
• Wilm's tumor	
• Rhabdomyosarcoma	
• Non-Hodgkin lymphoma	
• Adrenal cortical carcinoma	

HEPATOBLASTOMA

Hepatoblastoma (HB) is the most common primary malignant liver tumor in children with a reported incidence of 1.6–2 per million children in western countries. Nearly 70% of HBs are diagnosed within 2 years of age.

Etiopathogenesis

Most HBs are sporadic while some are associated with chromosomal abnormalities like loss of heterozygosity at 11p15.5 locus, trisomies such as 20, 2, 3, and rarely, 18. HB is associated with certain syndromes like Beckwith-Wiedemann, familial adenomatous polyposis (FAP)/Gardener, Li Fraumeni, Soto syndrome and neurofibromatosis type 1. Other associations include hemihypertrophy and adrenal agenesis. For unknown reasons, extreme prematurity and very low birth weight infants have a higher incidence of HB.

Specific mutations of the adenomatous polyposis coli (APC) gene are associated with HBs in FAP. Changes in the expression of *H19* and *IGF2* genes, genetic aberrations involving the *wnt* signaling pathway, hedgehog gene pathway, insulin-like growth factor axis and hepatocyte growth factor/c-met pathway are noted to be associated with HB. Telomerase activation, mutation of *CTNNB* or deletion of *CTNNB* exon 3 is found in a substantial proportion of HBs.

Pathology

Histologically HB is classified based on *International Consensus Classification Histologic Subtypes* (Table 2). Epithelial type accounts for 67% of all HBs, 7% are well-differentiated fetal type, and 5% are small cell undifferentiated tumors. Small cell undifferentiated tumors have a bad prognosis while there is not much of prognostic difference between the other subtypes.

Clinical Presentation

Most common presentation is a painless right upper quadrant abdominal mass. Liver-specific symptoms, such as cholestasis are extremely rare. Fever and anorexia may be present in advanced disease. There are case reports with hypoglycemia as presenting feature probably secondary to insulin like growth factor secreting tumors and isosexual precocity with beta-hCG secreting tumors. Tumor thrombus extending into the IVC or right atrium can present with features of outflow obstruction and heart failure. Tumor rupture is rare and can present with acute abdomen and anemia.

Diagnosis

When suspected of a liver tumor, the cost-effective initial imaging investigation would be ultrasonography of the abdomen.

Abdominal ultrasonography would give good information about extent of the lesion and discerns whether the lesion is solid or cystic and whether it is a solitary or a multifocal tumor. CT and MRI, utilizing appropriate contrast or vascular enhancement, are essential to determine the tumor extension and resectability. Before initiation of chemotherapy, it is recommended to have a CT scan of abdomen along with chest that would help in staging and formulating treatment plan.

Tissue diagnosis is essential before initiating chemotherapy and the only exception is an HB between 6 months and 3 years of age if imaging is typical with high alpha fetoprotein (AFP). The biopsy can be done either percutaneously under ultrasound guidance or by open surgical technique. AFP levels are elevated in more than 90% of children with HB. AFP less than 100 at diagnosis is associated with poor prognosis. Serial levels are helpful in monitoring tumor response to chemotherapy.

Hepatoblastoma Staging

Several staging systems exist for HB of which presurgical pretreatment extent of disease (PRETEXT) staging devised by the Société Internationale d'Oncologie Pédiatrique-Epithelial Liver Tumor Study Group (SIOPEL) is gaining wide acceptance. This staging system was found to be superior in predicting resectability of tumors and outcome, when compared to Tumor Node Metastasis (TNM) or Children Oncology Group (COG) postsurgical-based staging system staging. The SIOPEL suggests neoadjuvant chemotherapy followed by definitive surgery, while the COG suggests primary tumor resection whenever possible.

Liver is divided into four sectors (Fig. 1): (1) Couinaud segments 5 and 8 constitute the right anterior sector, (2) segments 6 and 7 constitute the right posterior sector, (3) segments 2 and 3 constitute left lateral, and (4) left medial sector consists of segments 4a and 4b. PRETEXT staging is based on these sectors. Caudate lobe is given separate staging consideration as extrahepatic disease, tumor focus, tumor rupture, distant metastasis, lymph node involvement, portal, hepatic and inferior vena cava (IVC) involvement (Table 3).

Management

Chemotherapy remains the cornerstone in management of HB. SIOPEL group was formed under the auspices of International Society of Pediatric Oncology in 1987, and has completed three major international collaborative studies in pediatric liver tumors in the process to improve the survival outcome in HB with minimal side effects of chemotherapy (Box 1). Primary resection has been recommended for resectable tumors in USA, while SIOPEL recommend downstaging the tumors with chemotherapy and then to resect. Tumors that were deemed to be unresectable (unifocal PRETEXT 4) have been found to be resectable after

Table 2 International consensus classification histologic subtypes of hepatoblastoma

Monomorphic	Mixed
Epithelial	Teratoid
Fetal:	Stromal derivatives:
• Well-differentiated	• Chondroid
• Crowded or mitotically active	• Osteoid
• Pleomorphic, poorly differentiated	• Skeletal muscle
• Anaplastic	
Embryonal	
Macrotrabecular	
Small cell undifferentiated	
Cholangioblastic	

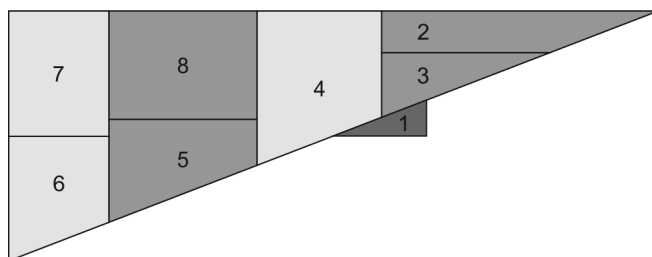


Figure 1 Schematic diagram of liver showing four sectors: (1) Couinaud segments 5 and 8 constitute the right anterior sector, (2) Segments 6 and 7 constitute the right posterior sector, (3) Segments 2 and 3 constitute left lateral and (4) Left medial sector consists of segment 4

Table 3 PRETEXT staging of hepatoblastoma

Pretext 1	3 contiguous sectors are tumor-free
Pretext 2	2 contiguous sectors are tumor-free
Pretext 3	1 sector tumor-free
Pretext 4	No sector tumor-free
In addition, any group may have:	
V—	ingrowth into the IVC or all three hepatic veins involved
P—	ingrowth into portal vein or involvement of portal bifurcation
E—	extrahepatic contiguous tumor
C—	involvement of caudate lobe
M—	distant metastases

BOX 1 SIOPEL trials on hepatoblastoma and outcome**SIOPEL 1**

All HBs were subjected to preoperative chemotherapy (neoadjuvant) with cisplatin and doxorubicin—termed as PLADO. Each cycle comprised of cisplatin (80 mg/m²) given as a 24-hour IV continuous infusion and doxorubicin (60 mg/m²) as a continuous 48-hour IV infusion. Four cycles are given at 3 weekly intervals followed by either resection or liver transplantation and the chemotherapy course is completed with further two cycles. In case of unresectability at the end of four cycles, reassessment was done after further two cycles.

Overall survival rates were as follows:

100% for PRETEXT 1; 91% for PRETEXT 2; 68% for PRETEXT 3; 57% for PRETEXT 4 and 25% for patients with metastasis.

SIOPEL 2

SIOPEL 2 trial was designed to test the efficacy and toxicity of two chemotherapy regimens. HB was stratified into either *standard risk* and *high-risk* at diagnosis based on tumor confined to liver with at least one tumor-free sector (PRETEXT 1, 2 and 3) or PRETEXT 4/extrahepatic extension/metastasis/serum AFP < 100 units, respectively. Standard risk patients were treated with cisplatin monotherapy and high-risk patients treated with cisplatin alternating with carboplatin and doxorubicin, referred to as *Super PLADO* regimen, preoperatively and postoperatively. Overall 3-year progression-free survival rates were 89% and 48%, for standard and high-risk respectively.

SIOPEL 3

SIOPEL 3 trial prospectively compared either cisplatin alone or PLADO for standard risk tumors and SUPER PLADO for high-risk tumors. The results for SIOPEL 3 for *standard risk* patients confirmed that Cisplatin monotherapy is as effective as PLADO in this standard risk group of patients. SUPER PLADO for high-risk tumors showed increased resectability.

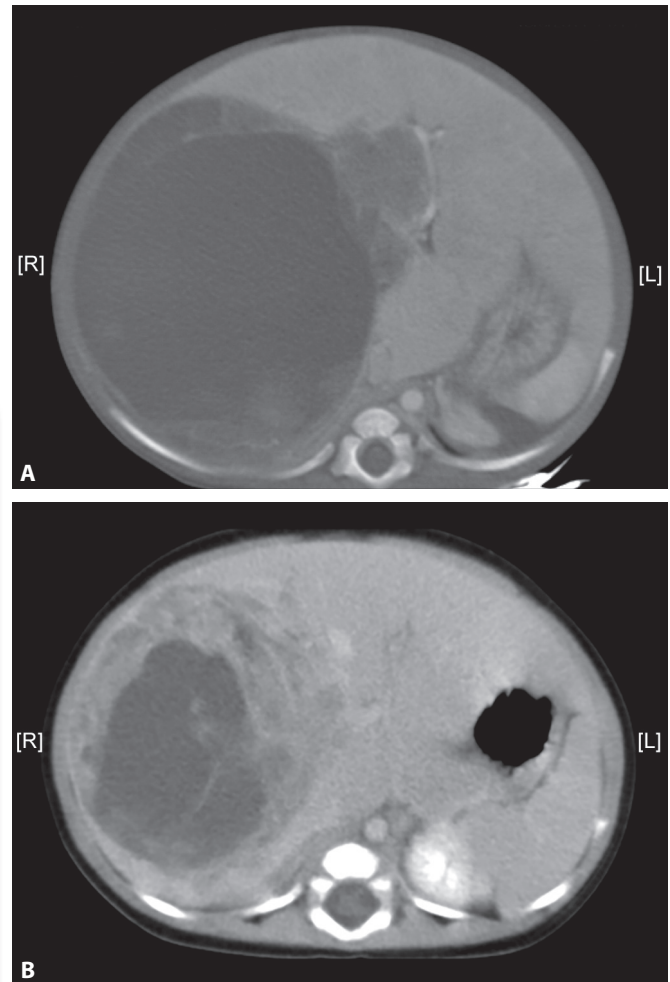
SIOPEL 4

SIOPEL 4 study is underway looking at outcome of high-risk patients with a more intensified chemotherapy employing doxorubicin and cisplatin during preresection and doxorubicin and carboplatin were employed for unresectable tumors and for postresection.

Relapse or resistant tumors:

Other chemotherapeutic agents like irinotecan, topotecan, ifosfamide, etoposide, and certain newer drugs like ixabepilone, gemcitabine and bevacizumab are being tried in relapsing or recurrent tumors.

chemotherapy (**Figs 2A and B**), this is due to the fact that the tumor can stretch the lateral margin and could bulge into the adjacent sector without actually infiltrating it. Usually surgery is planned after four cycles of chemotherapy, but if the tumor is deemed to be unresectable on imaging, further two cycles of chemotherapy are given and reassessed. Downstaging using chemotherapy before surgery helps in better demarcation of anatomical margins and likelihood of having complete resection. In our experience, we have seen tumors with extensive osteoid formation (**Fig. 3**), which did not regress in size with chemotherapy and so resection



Figures 2A and B (A) Large hepatoblastoma at the time of presentation; and (B) Tumor regression after four cycles of chemotherapy

was attempted after six cycles. But resected specimen showed only 5% viable tumor cells, which indicate good response to chemotherapy and this tumor could have been resected after four cycles. Response to chemotherapy should be guided by serial fall in AFP rather than shrinkage in tumor size.

Surgery

Surgical resections would include segmentectomy (single involved segment is removed); hemihepatectomy (either right or left lobe); extended right hepatectomy (only segment 2, 3 and caudate lobe are left behind); extended left hepatectomy (most of segments 5 and 8 are removed along with the left lobe); or central hepatectomy (resection of Couinaud's segments 4, 5, and 8). Children tolerate extensive resection even unto 75% of liver mass, as the remaining liver is non-cirrhotic with well preserved synthetic function. Such extreme surgeries have to be carried out in centers with transplant facilities.

Liver Transplant

Liver transplantation is offered in case of unresectable central tumors or PRETEXT 4 tumors. Primary liver transplantation has a better outcome compared to rescue liver transplantation due to incomplete partial resection or relapse after partial hepatectomy. Ten-year survival after primary liver transplantation is around 85% while with rescue liver transplantation, the survival is only 40%, and, therefore, heroic resections should not be attempted. Lung metastasis and macroscopic extension into the portal vein and/or

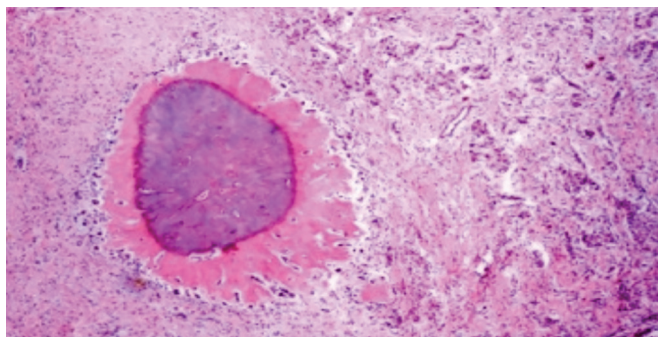


Figure 3 Histology in hepatoblastoma showing extensive osteoid formation with mineralization

the hepatic veins/vena cava are only relative contraindications for liver transplantation.

HEPATOCELLULAR CARCINOMA

Hepatocellular carcinoma (HCC) is the most common hepatic malignancy in adults while in children it is the second most common malignancy following HB.

Etiopathogenesis

In contrast to adults where HCC is seen in 80–90% cirrhotic population, only one-third of children have underlying cirrhosis. In children, certain cirrhotic metabolic disorders such as tyrosinemia and progressive familial intrahepatic cholestasis (PFIC) predispose to HCC at very young age. HCC secondary to chronic hepatitis B or C infection occurs in older children. Glycogen storage disease type 1, porphyria, alpha-1-antitrypsin deficiency are few of the other metabolic disorders with increased risk of HCC. Around 40% of children with tyrosinemia develop HCC and this is probably due to mutagenic effect of toxic intermediate compounds such as maleylacetoacetate and fumarylacetoacetate. Nitro trifluoromethyl benzoyl cyclohexanedione, popularly known as NTBC, which is used in the treatment of tyrosinemia, does not reduce the risk of HCC if introduced after 6 months of life. Genetic disorders such as neurofibromatosis and FAP are associated with higher incidence of HCC.

Detailed molecular mechanisms of evolution of HCC are largely unknown. Active inflammation and oxidative damage are the key events. A multihit model with cumulative genetic changes leading to high-grade dysplastic changes in hepatocytes, which lead onto HCC in a time span of 5 years, has been proposed. Intense neoangiogenesis occurs during this transition. An 8q copy gain, down regulation of p5, abnormal regenerative signaling from the sick cells to younger regenerating hepatocytes are few of the proposed mechanism of carcinomatous transformation.

Pathology

Hepatocellular carcinoma can be categorized as *classic* or *fibrolamellar* based on histological characteristics. *Classic HCC* reveals large polygonal cells with central nuclei, frequent mitotic figures and often invasion into surrounding hepatic tissue. Tumor cells in the *fibrolamellar variant* are circumscribed characteristically by bundles of acellular collagen, creating either trabeculae or large nodules of tumor islands. Immunostaining recognizes cytokeratin 7, 8, 18 and 19, chorioembryonic antigen and AFP. Classic type is usually seen in cirrhotic liver, while fibrolamellar variant, which does not have a favorable prognosis, is seen in noncirrhotic liver. Usually HCC appears as a distinctive nodule and as the tumor size increases, portal veins could get involved and the tumor could spread to lymph nodes, adrenals, lungs and bones.

Clinical Features

The initial presentation could be an abdominal mass, weight loss, anorexia, pain, and rarely, jaundice. The diagnosis might be delayed in noncirrhotic disease, as regular surveillance tends to pick-up HCC early in cirrhotic children. Tumor rupture or bone metastasis may be the presenting symptom in a few children. Paraneoplastic manifestations can include diarrhea, hypoglycemia, hypercalcemia secondary to excess production of parathyroid hormone-related protein (PTH-rP), hyponatremia secondary to excess antidiuretic hormone (ADH), polymyositis, thrombophlebitis and skin rashes.

Diagnosis

Ultrasonography would show HCC as a nodule and might be difficult to differentiate it from regenerating nodule or an adenoma. Contrast enhanced ultrasound (CEUS) is a helpful screening technique, as it would differentiate HCC from regenerative nodules. Differentiation of cirrhotic nodules from HCC requires a contrast CT or a dynamic MRI. The presence of intense arterial uptake of contrast (consistent with extensive neoangiogenesis within the tumor) followed by washout in venous phase is highly specific for HCC (**Figs 4A and B**). Biopsy is necessary in nodules exhibiting atypical vascular pattern on contrast CT.

American Association of Study of Liver Disease (AASLD) does not recommend AFP as a surveillance tool in HCC as it lacks sensitivity and specificity to diagnose the condition. Tyrosinemia is a condition where there is an associated raised AFP levels, and any increase from the usual baseline should raise the suspicion of malignant transformation of a nodule. Other tumor markers like lectin bound AFP, des-gamma-carboxy prothrombin and glypican are being studied.

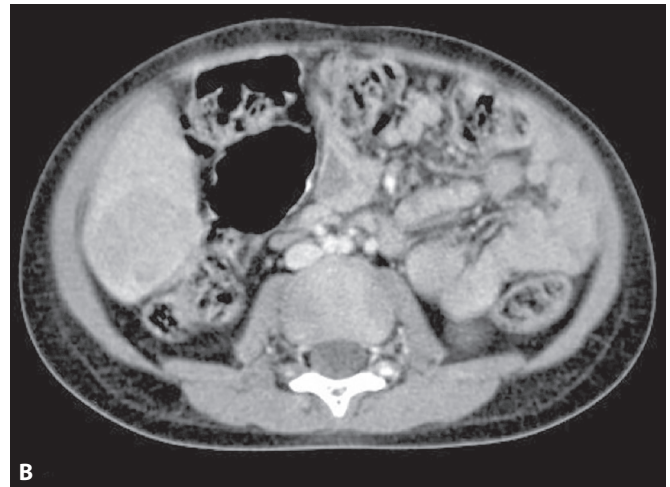
Staging

There is no widely accepted single staging system for pediatric HCC. Okuda classification, TNM staging, Barcelona Liver Clinic Staging (BLCS), Japanese Integrated Scoring, PRETEXT, etc., have been used in adults. BLCS system, which takes into account tumor size, liver function test, and physical condition of the patient was found to be helpful in formulating appropriate management pathway in HCC, and widely used.

Treatment

Several chemotherapeutic agents, such as cisplatin, doxorubicin, vincristine, 5-fluorouracil, etc., have been used with unsatisfactory results. Complete tumor resection remains the corner stone in management, but is feasible only in few because a small HCC nodule can be resected successfully only in a noncirrhotic liver. Cirrhotic liver will have dysplastic nodules in the leftover segments, which could turn malignant and also there is high probability of postoperative liver failure. The Milan criteria was introduced in 1996, to select adults with HCC for a better outcome which includes (a) single tumor diameter less than 5 cm; (b) not more than three foci of tumor, each one not exceeding 3 cm; (c) no angioinvasion; and (d) no extrahepatic involvement. Since the introduction of these criteria, long-term recurrence-free survival after liver transplant in adults with HCC improved from 30% to 75%. In children, where most of the HCC is *de novo* with tumors having different biological and genetic behavior, use of the Milan criteria is questioned. Reported pediatric series has shown that neither the size of tumors, nor the presence of gross vascular invasion were associated with post-transplant tumor recurrence. So, most centers offer liver transplantation to children with large *de novo* HCC, provided there is no extrahepatic involvement.

Percutaneous ethanol ablation (PEA) or radiofrequency ablation (RFA) is reserved for early HCC, where resection is not feasible. RFA is preferred for tumors less than 2 cm, while PEA is



Figures 4A and B (A) Intense uptake of contrast during arterial phase; (B) Tumor washout when compared with the surrounding during venous phase is very typical of hepatocellular carcinoma

preferred for tumors more than 2 cm, tumors close to the biliary tree, abdominal organs or the heart.

Regional chemotherapy (doxorubicin, mitomycin, or cisplatin) in the form of transarterial chemo embolization (TACE) can be tried in unresectable tumors or to downsize the tumor while patient is waiting for transplantation. Apart from providing regional chemotherapy with minimal systemic risks, embolization of feeding arteries may increase the dwell time of chemotherapeutic agents at the tumor site. Temporary or permanent embolizing materials like embocept/lipiodol/stainless steel coils can be used. Sorafenib is an oral multikinase inhibitor. It inhibits Raf kinase and several other tyrosine kinases (VEGF receptor 2, PDGF receptor, and c-kit receptors), thereby inhibiting angiogenesis and cell proliferation. It is used in unresectable tumor as palliative therapy and found to have prolonged the survival.

OTHER TUMORS

Focal nodular hyperplasia (FNH) is rare in children and remains asymptomatic, although some patients present with an abdominal mass or pain. As the name suggests the lesions have features of a well-localized area of liver cell hyperplasia around a fibrous scar. Presence of this central fibrous scar in CT or MRI scans is diagnostic of FNH. Surgical management is required only in patients with pressure symptoms. These tumors do not turn malignant.

MORE ON THIS TOPIC

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IN A NUTSHELL

1. Hemangiomas and hamartomas are the most common benign liver tumors, while HB is the most common primary malignant liver tumor in children.
2. Hepatocellular carcinoma is the most common hepatic malignancy in adults while in children, it is the second most common malignancy following HB.
3. Childhood liver tumors are unique in the sense that some tumors like large hemangioendothelioma could involute spontaneously without treatment, while a small HCC may warrant liver transplantation.

Section 38 DISORDERS OF HEMATOPOIETIC SYSTEM

Section Editor VP Choudhry

Chapter 38.1

The Hematopoietic System

Praveen C Sobti, Shruti Kakkar

Blood is a vital body fluid composed of red blood cells (RBCs), white blood cells and platelets suspended in plasma. All the components play important functions in our body. RBCs carry oxygen to all vital organs; white blood cells are involved in body's defense mechanism and platelets play an important role in blood clotting.

All the cellular components of blood are derived from a pluripotent hematopoietic stem cell (PHSC). PHSC is characterized by its ability of self-renewal and differentiation. The process of formation of mature blood cells from PHSCs is known as hematopoiesis. Hematopoiesis involves a series of steps in which progressively lineage specific cells are produced from undifferentiated stem cells. Around 200 million RBCs, 10 million white blood cells and 400 million platelets are produced by the hematopoietic system every day. The basic understanding of development of the hematopoietic system is vital for understanding the pathophysiology of various hematological disorders (**Fig. 1**).

SITE OF HEMATOPOIESIS

Hematopoiesis begins in human beings as early as 3rd week of gestation. The vascular as well as the hematopoietic system develops from mesodermal cell aggregates in the extraembryonic yolk sac from a common precursor called "hemangio-endothelioblast". After originating in the yolk sac, hematopoiesis occurs sequentially in AGM (aorta, gonad and mesonephros region) and placenta, liver, thymus and spleen, before finally settling in bone marrow (**Figs 2A and B**). Bone marrow continues to be the major site of hematopoiesis from 2nd trimester onwards well into the adulthood.

The initial wave of hematopoiesis arising from the yolk sac, known as primitive hematopoiesis, produces mainly erythrocytes with few macrophages and megakaryocytes (MKs). The next wave of hematopoiesis arises in AGM, blood vessels and placenta. The PHSCs in this region arise de novo or migrate from yolk sac is not clear. The hematopoietic progenitors migrate from AGM region to liver during this phase and produces both erythroid and myeloid cells.

Yolk Sac

The hematopoietic stem cells originate from a mesodermal cell cluster. The cells present centrally disappear to give rise to vascular lumen and cells at the periphery undergo transformation to acquire the properties of endothelial cells. There are small clumps of cells present along the primitive endothelium known as blood islands which form the initial site of hematopoiesis (**Fig. 3**). Both the endothelial and the hematopoietic cells express CD-34 suggesting

a common cell of origin. With the onset of cardiac activity, the yolk sac derived hematopoietic progenitor cells are carried to liver through blood circulation. By day 60, hematopoiesis disappears from the yolk sac.

Liver

Hematopoietic cells do not arise de novo in liver; the yolk sac derived progenitor cells differentiate and mature into the blood elements. The shift in site of hematopoiesis is also accompanied by the switch in the hemoglobin from embryonic to fetal. There is also a change in erythrocyte morphology; definitive macrocytes are formed instead of primitive megaloblasts. Liver remains the major site of hematopoiesis till the 2nd trimester and continues producing cells till 2nd week of postnatal life.

Bone Marrow

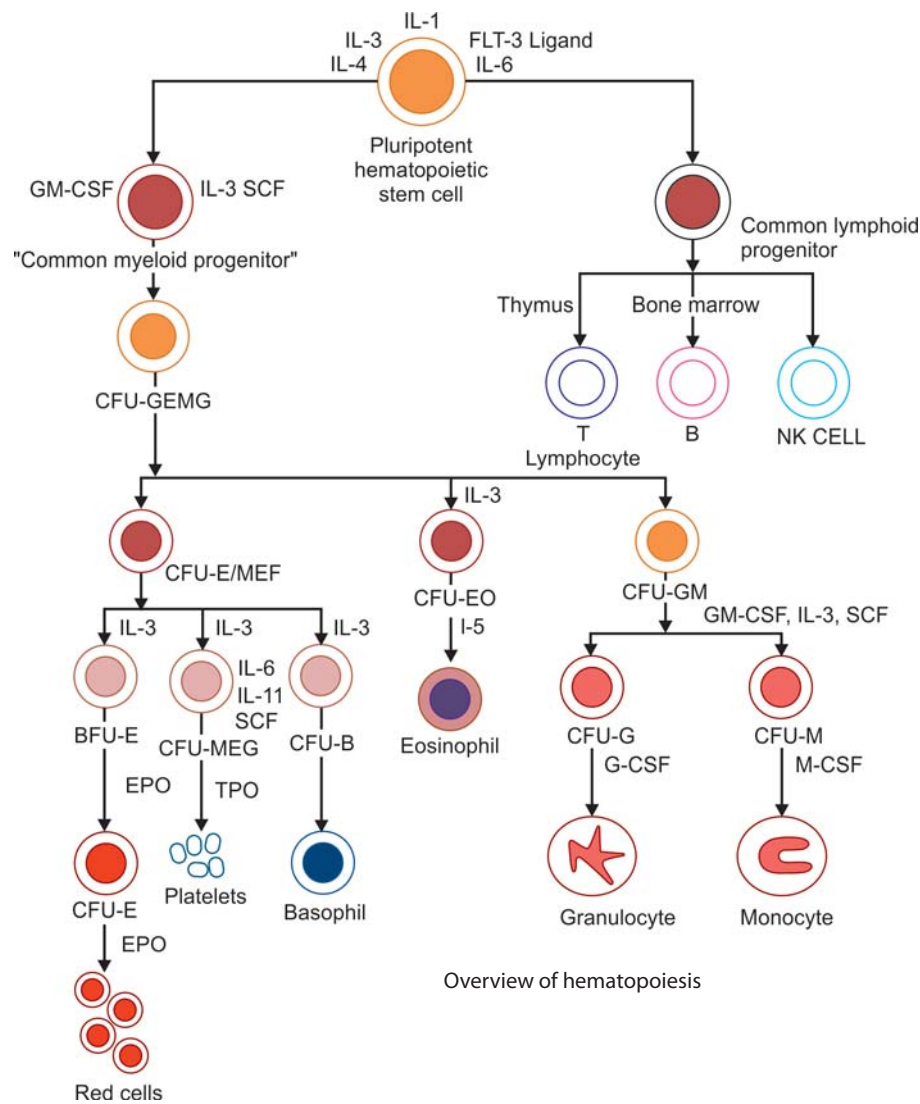
Hepatic hematopoiesis starts declining from the 2nd trimester as the PHSCs settle in the bone marrow and start producing mature blood cells. The ability of the bone marrow to support indefinite hematopoiesis rests in a small pool of PHSCs. In infancy, whole of the bone marrow is active but the hematopoiesis remains restricted to the flat bones and proximal end of femur and humerus in the adult life (**Fig. 2B**). In hemolytic anemia, hematopoiesis can expand to all the bones as well as extramedullary organs (liver and spleen) as in fetal life. T-cells are produced in thymus in embryonic, fetal and adult life.

PLURIPOTENT HEMATOPOIETIC STEM CELL

Hematopoietic stem cell (HSC) is the source of millions of blood cells produced per day. HSC is characterized by its properties of self-renewal and differentiation. HSC lack the cell surface markers expressed by the mature blood cells but express high level of Sca-1 and c-kit. This population of cells that lack the lineage specific markers and express Sca-1 and c-kit are referred to as LSK compartment ($\text{Lin}^-/\text{Sca-1}^+/\text{c-kit}^+$). HSC can be divided into long-term HSC (LT-HSC) and short-term (ST-HSC) reconstituting HSC. LT-HSCs are capable of sustaining lifelong hematopoiesis owing to their extensive self-renewal capacity whereas ST-HSC can sustain hematopoiesis for a short while only. HSCs undergo two types of differentiation: symmetric and asymmetric. In symmetric division, both the daughter cells retain the properties of stem cells. In asymmetric division, one of the daughters retains the property of self-renewal whereas the other one either undergoes differentiation to form a mature blood cell or can undergo apoptosis.

Stem Cell Niche

Stem cell niche refers to the microenvironment that the stem cells inhabit. The stem cell niche apart from providing anatomical space for the growth of stem cells also interacts with the stem cells and provides signals for self-renewal and differentiation. Two HSC niches have been identified in the bone marrow: the perivascular and endosteal niche.



Overview of hematopoiesis

Figure 1 The hematopoiesis involves a series of steps in which differentiated and mature cells are formed sequentially

Abbreviations: CFU-GEMM, colony-forming unit-granulocyte, erythroid, megakaryocyte, monocyte; BFU, burst forming unit; CFU, colony-forming unit; G, granulocyte; M, monocyte; E, erythroid; MK, megakaryocyte; B, basophils; Eo, eosinophil; GEMM, granulocyte, erythroid, megakaryocyte, monocyte; SCF, stem cell factor; EPO, erythropoietin; TPO, thrombopoietin; CSF, colony-stimulating factors; IL, interleukin.

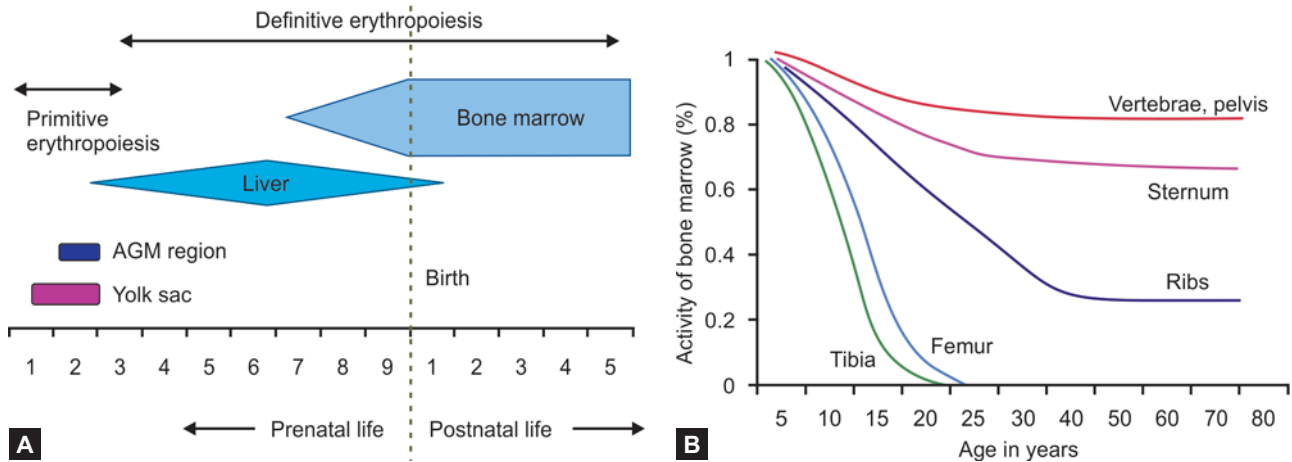
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The endosteal niche is composed primarily of osteoblasts. The perivascular niche is composed of endothelial cells, mesenchymal stem cell, CAR cells (CXCL12-abundant reticular cells), Schwann cells and the stromal cells (**Fig. 4**). It has been suggested that the endosteal niche maintains the HSC in quiescence and cells migrate to the perivascular niche to divide and proliferate. The osteoblasts secrete a variety of signals like angiopoietin 1, transforming growth factor- β (TGF- β), stem cell factor (SCF) for the maintenance of the stem cell pool. The stem cell niche also seems to be controlled by the stem cells as demonstrated by the role of regulatory T-cells in maintenance of allogeneic HSC even if no preparative chemotherapy is given.

ERYTHROPOIESIS

Erythropoiesis occurs in two phases, primitive and definitive, during the fetal life. Primitive erythropoiesis begins in the yolk

sac derived primitive erythroid progenitors. These erythroid progenitors enter the blood stream and mature in the circulation. Primitive erythropoiesis is characterized by the expression of the embryonic hemoglobin chains. Along with primitive erythroblasts, small population of circulating nucleated cells called pyrenocytes are also found in the circulation. These cells resemble the extruded nucleus of the late-erythroblasts and are rapidly engulfed by the macrophages (**Figs 5A and B**). Definitive erythropoiesis occurs in fetal liver after the 6th week of gestation. The earliest committed red cell precursor identified is a burst forming unit-erythroid (BFU-E). These slowly proliferating cells then give rise to mature BFUs which rapidly differentiate into CFU-E (colony forming unit-erythroid). The CFU-E undergoes cell division and differentiation over 2–3 days to give rise to a mature RBC. There is a progressive decrease in the cell size, chromatin condensation, increasing hemoglobin accumulation and finally leading to expulsion of the nucleus (**Fig. 6**).



Figures 2A and B Sites of erythropoiesis: (A) Different sites of erythropoiesis during prenatal and postnatal life (AGM: aorta, gonad and mesonephros region); (B) Hematopoietic activity of bone marrow of various bones. Hematopoietic activity in the bone marrow of long bones decreases with age and is virtually absent by 3rd decade of life. Bone marrow of vertebra, sternum and pelvis remains active throughout life. Adapted with permission from: Papayannopoulou T, Migliaccio AR. Biology of erythropoiesis, erythroid differentiation and maturation. In: Hematology: Basic Principles and Practice, 6th ed. Philadelphia, PA, USA: Saunders-Elsevier; ©Elsevier.

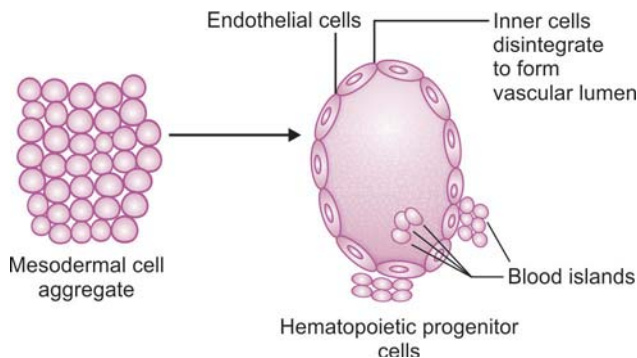


Figure 3 Development of PHSC from mesodermal cell aggregates. The vascular and hematopoietic system develops from a mesodermal cell aggregate in extraembryonic yolk sac. The cells in the periphery transform into endothelial cells and the inner cells disintegrate to form vascular lumen. PHSC develops from a collection of cells called blood islands

Abbreviation: PHSC, pluripotent hematopoietic stem cells.

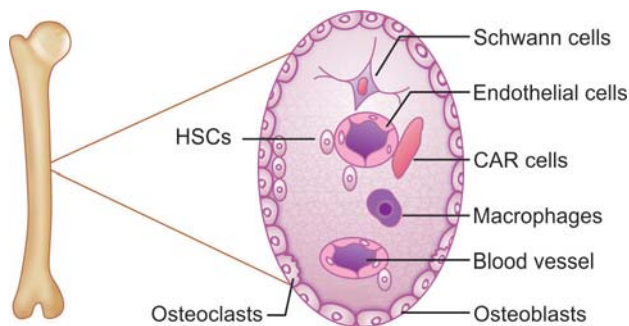
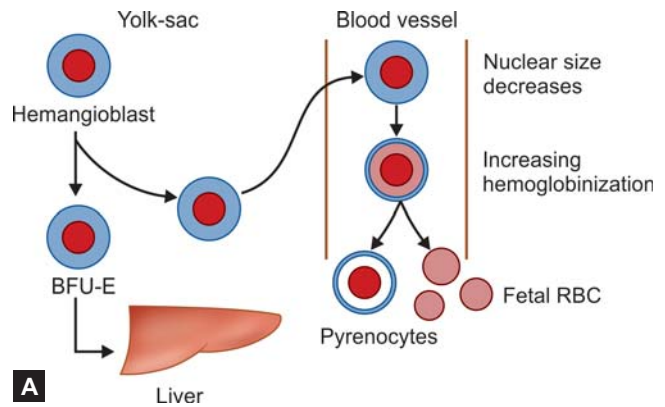
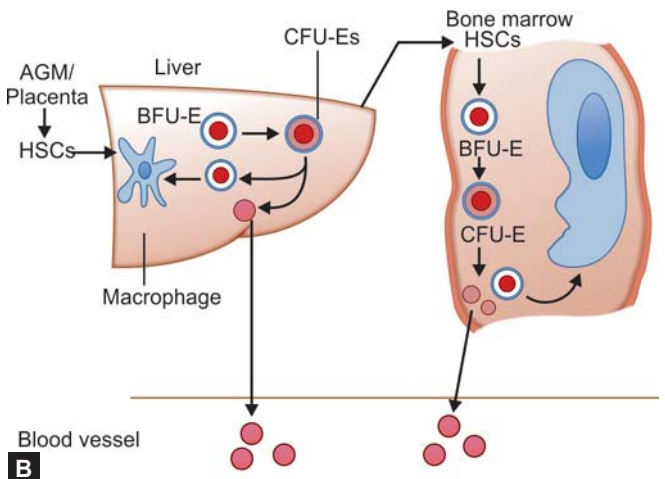


Figure 4 Hematopoietic stem cell niche. There are two stem cell niches: the endosteal niche and the perivascular niche. The osteoblasts constitute the endosteal niche. The perivascular niche is composed of perivascular endothelial cells, Schwann cells, macrophages and CAR cells

Abbreviation: CAR, CXCL12-abundant reticular cells.



A



B

Figures 5A and B (A) Primitive erythropoiesis in yolk sac. The differentiation erythroid precursors and formation of mature RBCs occurs within the vascular lumen; (B) Definitive erythropoiesis in liver and bone marrow. The entire process of hematopoiesis occurs within the marrow and mature RBCs are released into the circulation. Abbreviations: RBCs, red blood cells; AGM, aorta, gonad and mesonephros region; BFU, burst-forming unit; CFU, colony-forming unit; E, erythroid; HSC; hematopoietic stem cell.

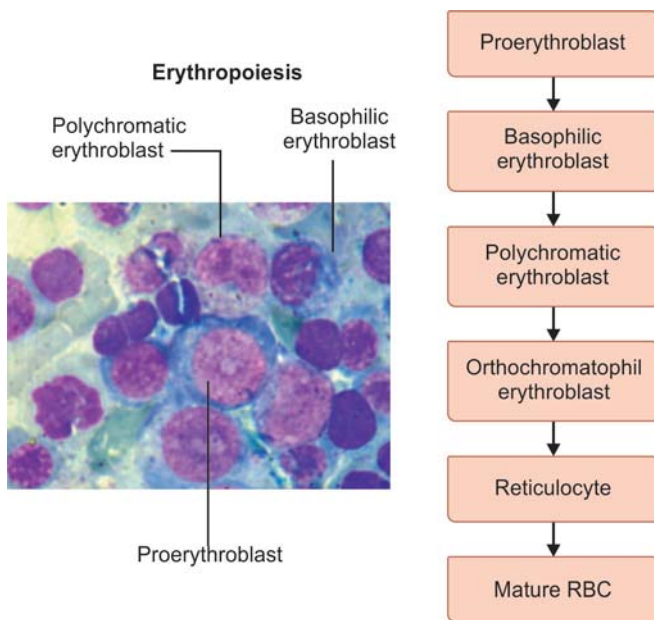


Figure 6 Stages of erythropoiesis: The proerythroblast undergoes a series of changes to form mature red blood cells (RBCs). The hemoglobin (Hb) content increase slowly and the nuclear size decreases with each step, before being extruded finally

Regulation of Erythropoiesis

Erythropoiesis is controlled by various extra- and intracellular factors. Extracellular factors include cytokines, hematopoietic growth factors and extracellular matrix. Various transcriptional regulators and microribonucleic acids (mRNAs) also control erythropoiesis.

Extracellular Factors Controlling Erythropoiesis

Erythropoiesis in fetal life is regulated by the growth hormones produced by the fetus itself and not by maternal growth factors. Erythropoietin (EPO) regulates the erythroid precursors in fetal, neonatal and adult life. The EPO in adults is secreted by the kidneys in response to hypoxia whereas liver appears to be the main source of EPO in the fetus. EPO is produced in the liver by cells of monocytic and macrophage lineage. The switch of EPO production from liver to kidney starts at about 130 days of gestation and completes by 40 days of postnatal life.

Erythropoietin is a glycoprotein (molecular weight 34,000) secreted in response to low oxygen levels. It has a globular three-dimensional structure with 3N-linked polysaccharide and one O-linked group. EPO is secreted as a 198 polypeptide residue from EPO messenger RNA (mRNA), and then undergoes cleavage of an arginine residue at carboxy terminus followed by glycosylation in the Golgi apparatus. The final product is a 166 polypeptide, consisting of 4 α helices stabilized by disulfide bridges. The half-life of EPO in plasma is approximately 7–8 hours. EPO binds to EPO-receptors (EPO-R) on the surface of erythroid progenitor cells. The initial stages of erythropoiesis are highly EPO-dependent, EPO-Rs are gradually lost as more and more mature erythroid cells are formed.

Erythropoietin-R is present on the erythroid progenitors as a homodimer. EPO binding to EPO-R produces conformational change; the intracellular domains move closer resulting in phosphorylation of Junas kinase-2 (JAK-2) kinases and initiation of signal transduction leading to erythropoiesis (Fig. 7). The

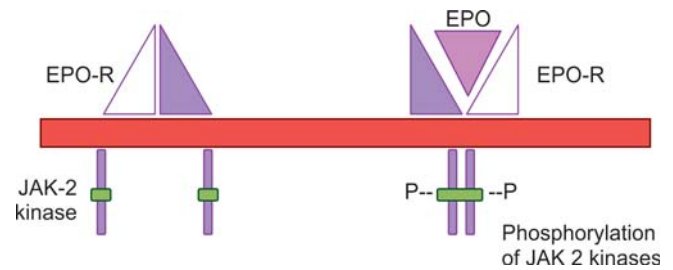


Figure 7 Erythropoietin (EPO). The EPO receptor (EPO-R) belongs to the cytokine family of receptors. The binding of EPO results in homodimerization of the receptor, resulting in phosphorylation of JAK-2 kinases present on the intracellular domain of EPO receptor. The phosphorylation of JAK-2 kinases results in activation of multiple intracellular pathways and transcription factors

signal transduction pathways triggered are signal transducer and activator of transcription 5 (stat 5), phosphoinositide-3 kinase/Akt, Shc/Ras/mitogen-activated protein kinase (MAPK) pathway.

Extracellular matrix protein, fibronectin, plays an important role in terminal differentiation and enucleation of the erythrocytes. Fibronectin fragments interact with the $\alpha_4\beta_1$ integrin on the erythroid progenitors.

Transcriptional Regulators of Erythropoiesis

A number of transcriptional regulators, like GATA-1, SCL/Tal-1, LMO-2, are involved in synthesis of micro-RNAs. Micro-RNAs are small regulatory RNAs which downregulate the expression of their target genes. These play an important role in erythropoiesis and regulate various steps, like erythroid-lineage determination, erythroid-progenitor proliferation and differentiation, chromatin condensation and enucleation (Table 1). GATA-1 is a member of zinc finger transcription family that binds to (A/T) GATA (A/G). It has two zinc fingers: one at carboxy terminus which binds to DNA and other at aminoterminal that stabilizes the interaction. GATA-1 is expressed by erythroid, megakaryocytic, eosinophilic, mast and multipotent progenitor cells. Loss of GATA-1 has been shown to result in severe anemia and arrest in erythropoiesis in murine models along with defects in megakaryocytic development. GATA-1 interacts with a wide range of proteins including FOG-1 (friend of GATA), LMO-2, EKLF/Spl and PU-1 for regulation of erythropoiesis.

Table 1 Role of micro-RNAs in erythropoiesis

mRNA	Target	Role
miR-150	MYB	Induces differentiation of megakaryocytic lineage and suppresses erythroid lineage
miR-221 and 222	KIT	Downregulation necessary for terminal differentiation of erythroid progenitors
miR-24	ALK4	Downregulation necessary for terminal differentiation of erythroid progenitors
miR-223	LMO-2	Downregulation necessary for terminal differentiation of erythroid progenitors
miR-144	Klf4	Required for β globin gene expression
miR-451	GATA-2 14-3-3 zeta	Required for steady state erythropoiesis
miR-15a	MYB	Increased expression of fetal hemoglobin gene expression
miR-191	Riok3 and Mxi 1	Downregulation required for chromatin condensation and enucleation of erythrocytes

Hemoglobin and its Variants

Hemoglobin is an iron-containing protein which carries oxygen in the RBCs (**Fig. 8**). Hemoglobin synthesis begins in the proerythroblasts and continues up to reticulocyte stage. The synthesis starts with the binding of succinyl CoA (derived from Krebs metabolic cycle) with glycine. The resultant pyrrole ring thus formed combine to form protoporphyrin IX. Iron is incorporated into the protoporphyrin IX to form heme molecule. Heme molecule joins with polypeptide chain to form hemoglobin chains. The hemoglobin chains are named after the polypeptide derivative as α , β , γ , δ , ϵ , etc. Hemoglobin is a tetramer composed of two α -like and two β -like chains. Various variants of hemoglobin are formed sequentially during the embryonic and fetal life before the production of adult hemoglobin (**Table 2**) which is controlled by two gene clusters; α gene cluster on chromosome 16 and β gene cluster on chromosome 11 (**Fig. 9**).

Embryonic hemoglobin is expressed in primitive erythroblasts developing in the yolk sac. It is composed of two ζ and two ϵ

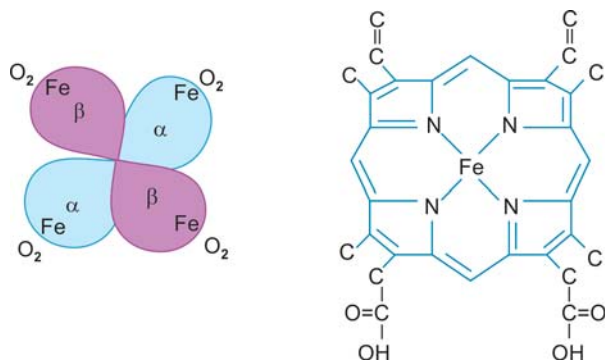


Figure 8 Structure of hemoglobin

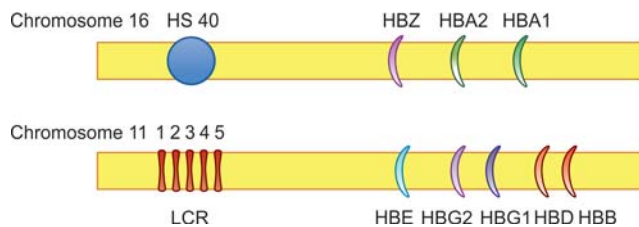


Figure 9 Hemoglobin gene locus. The α -like gene locus on chromosome 16 (5'- ζ - $\alpha 2$ - $\alpha 1$ -3'). The regulatory element HS 40 is located upstream. The β -like gene locus on chromosome 11 (5'- ϵ - γ - δ - β -3') controlled by five regulatory elements upstream which are collectively called locus control region (LCR)

Table 2 Different types of hemoglobin

Hemoglobin	α -like chain	β -like chain	Composition
<i>Embryonic</i>			
Gower 1	ζ	ϵ	$\zeta_2\epsilon_2$
Gower 2	α	ϵ	$\alpha_2\epsilon_2$
Portland	ζ	γ	$\zeta_2\gamma_2$
<i>Fetal</i>			
Hemoglobin F	α	γ	$\alpha_2\gamma_2$
<i>Adult</i>			
Hemoglobin A	α	β	$\alpha_2\beta_2$
Hemoglobin A2	α	δ	$\alpha_2\delta_2$

chains. As the site of hematopoiesis shifts from yolk sac to liver, the production of embryonic ζ and ϵ chains ceases. The production of α and γ chains increases leading to formation of fetal hemoglobin (HbF - $\alpha_2\gamma_2$). In human beings, two γ globin genes are present, $^G\gamma$ and $^A\gamma$, which differ in a single amino acid. The major switch in human hemoglobin happens perinatally, with decrease in HbF and formation of adult hemoglobin ($\alpha_2\beta_2$). The levels of HbF decrease after birth so as HbF constitutes 70% of hemoglobin at birth and falls to only trace levels by 6–12 months of age. Apart from adult hemoglobin HbA, HbA₂ ($\alpha_2\delta_2$) is also present in minor quantity in adult life (**Fig. 10**). In human erythrocytes, there is a very delicate balance between the α and β chains. The balance is maintained by regulatory elements present upstream the α and β gene clusters. In α gene cluster, there is a single element known as HS 40 where in β gene cluster, there are five such elements collectively known as locus control region (LCR). Various transcriptional regulators are involved in fetal-to-adult hemoglobin switch (**Table 3**).

Erythrocyte Indices During Fetal and Neonatal Life

- Hemoglobin (Hb)** Hemoglobin in a fetus of 10 weeks is 10.9 ± 0.7 g/dL and increases to 16.6 g/dL at 39 weeks of gestation.
- Mean corpuscular volume (MCV)** The MCV is a measure of average red cell volume. The MCV in a neonates delivered at 22 weeks is approximately 122 fL. MCV decreases with the gestational age and a newborn at term has an MCV of 105 fL. MCV reaches the adult value by 11th week of postnatal life.

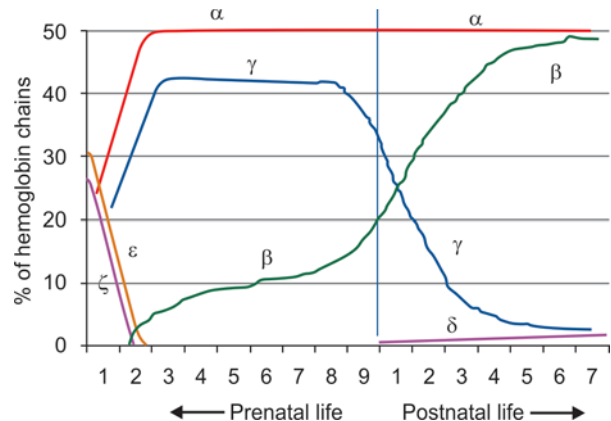


Figure 10 Sequential appearance of different hemoglobin (Hb) chains during pre- and postnatal life

Table 3 Transcriptional regulators of fetal to adult hemoglobin switch

Regulator	Role
BCL11A	Repressor of γ -globin gene expression
SOX6	Interacts with BCL11A to repress-globin gene expression
KLF1 (EKLF)	Repressor of γ -globin gene expression Haploinsufficiency results in HPFH
COUP-TFII orphan nuclear transcription factor	Binds to DR-like sequences in proximal γ -globin gene promoters Repressor of γ -globin gene expression
DRED (TR2/TR4) orphan nuclear transcription factor	Binds to DR1 sequences in proximal γ -globin gene promoters Repressor of γ -globin gene expression
FOP	Directly interacts with and is methylated by PRMT1 Regulator or repressor of γ -globin gene expression

- **Mean corpuscular hemoglobin (MCH)** The MCH measures the average hemoglobin content of the RBCs. The MCH, like MCV, decreases with the gestational age. The MCH falls from 40 pg for a neonate born at 22 weeks of gestation to 36 pg in neonate born at term.
- **Mean corpuscular hemoglobin concentration (MCHC)** MCHC does not change significantly with the gestational age.
- **Reticulocyte count** The reticulocyte count in fetus is approximately 4–8 times that of an adult. Neonates also have high reticulocyte count and red cell volume distribution width (RDW) owing to high erythropoietic activity. Reticulocyte count in a neonate is 3–7% and drops to 0.5–1% in 1st week of postnatal life. It reaches adult levels by 9th week of life.
- **Shape of RBCs** The RBCs in a neonate are heterogeneous. The lower the gestational age, higher is the percentage of abnormally shaped RBCs in circulation. In a neonate, 43% RBCs are disk-shaped and 40% are stomatocytes compared to 78% discocytes and only 18% stomatocytes in adults. In a term neonate, nucleated RBCs are rapidly cleared from the circulation so as no nucleated RBCs are found beyond 2–3 days of life whereas in a preterm neonate, it may take up to a week to clear nucleated RBCs from the circulation.

THROMBOPOIESIS

Platelet production begins in the fetus by approximately 5 weeks of gestation. The first committed MK precursor identified is BFU-megakaryocyte (BFU-MK). A single BFU-MK is capable of giving rise to 50 MKs. BFU-MK matures into a CFU-MK, which gives rise to 3–50 MKs. A MK is a unique cell as it undergoes endomitosis, the division in which nucleus undergoes duplication, but there is no cell division. The cells accumulate increasing deoxyribonucleic acid (DNA) content which can be as high as 128N. MKs are predominantly present in the bone marrow, but can be found in peripheral blood, lungs and spleen under stress. Mature MKs produce platelets by budding, i.e., forming elongated pseudopods called proplatelets (**Fig. 11**). The fetus achieves a platelet count of $150 \times 10^9/L$ by the end of 1st trimester. The platelet production occurs in four main steps.

Production of Thrombopoietic Factor

Thrombopoietin (TPO) is a polypeptide containing 332 amino acids synthesized in the liver. TPO, a c-MPL ligand, is the principle regulator of thrombopoiesis in fetus as well as adults. It stimulates all stages of MK precursors. TPO has been detected in fetus by 6 weeks of gestation. It is composed of two domains, receptor-binding domain and another carbohydrate rich domain which imparts stability to the compound. Binding of TPO to c-MPL results in dimerization of the receptor and activation of signal transduction pathways, like phosphatidylinositol 3-kinase (PIK3), Akt, MAPK and ERK 1 and 2. The circulating level of serum TPO is low (approximately 10 mol/L), but this can increase considerably in thrombocytopenic states. The plasma TPO concentration has been found to be inversely related to platelet levels. Platelets regulate plasma TPO levels by an autoregulatory loop. TPO is removed from circulation by the platelets. Hence, higher the number of platelets in circulation, lower is the plasma TPO level.

Proliferation of Megakaryocyte Precursors

As stated earlier, MKs are unique as they undergo nuclear division without cytoplasmic division, a process known as endomitosis. The endomitosis leads to accumulation of large quantities of mRNA and proteins. Protein tyrosine phosphatases Shp1 and Shp 2 have been discovered recently and thought to play an important role in endomitosis.

Megakaryocytes also produce a lot of granules which are necessary for functioning of the platelets by budding of small vesicles from Golgi apparatus. The different granules found in platelets are shown in **Table 4**.

Maturation of Megakaryocytes

As these MKs mature, they develop an intricate network of membrane system known as invaginated membrane system (IMS). The IMS retains contact with the extracellular space and divides the cytoplasm into small territories. Actin fibers provide the force for the formation of IMS via WASp/WAVE pathway. Recently, a *CDC42*-interacting protein 4 (CIP4) has also been found to play important role in cytoskeletal and membrane remodeling.

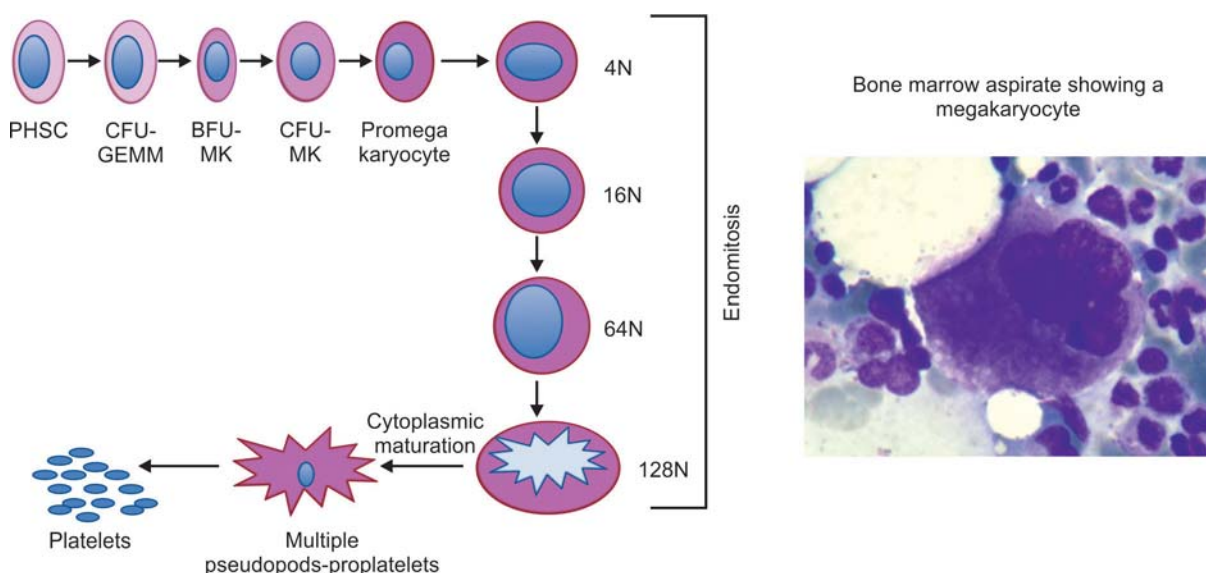


Figure 11 Megakaryocyte (MK) development

Abbreviations: PHSC, pluripotent hematopoietic stem cell; CFU-GEMM, colony-forming unit-granulocyte, erythroid, megakaryocyte, monocyte; BFU, burst-forming unit; CFU-Mk, colony forming unit megakaryocyte.

Table 4 Platelet granules: contents and functions

Granules	Content	Function
α granules	Hemostatic factors (e.g., Factor V, VWF, fibrinogen), angiogenic factors (e.g., angiogenin, VEGF), anti-angiogenic factors (e.g., angiostatin, PF4), growth factors (e.g., PDGF, bFGF, SDF1 α), proteases (e.g., MMP2, MMP9), necrotic factors (e.g., TNF- α , TNF- β)	Involved in adhesion of platelets to vessel wall, platelets
Dense granules	ADP, ATP, serotonin, calcium	Involved in platelet activation
Lysosomal granules	Lysosomal enzymes, e.g., glycosidases and proteases	Unclear

Abbreviations: VWF, von Willebrand factor; VEGF, vascular-endothelial growth factor; ADP, adenosine diphosphate; ATP, adenosine triphosphate; TNF, tumor necrosis factor.

Table 5 Differences between neonatal and adult platelets

Characteristic	Neonatal platelets	Adults platelets
TPO concentration	High	Low
Response to TPO	Highly sensitive	Less sensitive as compared to platelets of a neonate
Megakaryocyte progenitors	Increased number of CFU-MK and BFU-MK	Lesser number
Megakaryocytes	Small, lower ploidy Cytoplasmically mature Increased expression of GATA-1 and surface GP-1	Larger, higher ploidy Decreased expression
Platelets	Reticulated platelets present	Absent

Abbreviations: TPO, thrombopoietin; CFU-MK, colony-forming unit megakaryocyte; BFU-MK, burst forming unit megakaryocyte.

Release of Platelets

Once mature, MKs form proplatelets from its membrane. The microtubules containing polymers of $\alpha\beta$ tubulin are important for formation of the proplatelets. MKs extend pseudopods, which taper and elongate to form proplatelets shaft measuring 2–4 μ m. Whole of the MK cell body transforms into proplatelets, the nucleus is then extruded and degraded. These proplatelets are then released into the sinusoidal blood vessels in the bone marrow and form platelets.

The fetal thrombopoiesis differs from adult thrombopoiesis. Fetal thrombopoiesis is characterized by a higher number of reticulated platelets, higher level of TPO and increased sensitivity to TPO. Fetal MKs are smaller, have lower ploidy and more cytoplasmically mature than adult MKs. Also, the fetal MKs have increased expression of GATA-1 and surface glycoprotein-1. The BFU-MK and CFU-MK are present in greater numbers in fetal life and decrease gradually after birth (**Table 5**). These differences between the fetal and adult platelets resolve in the 1st postnatal month.

FETAL MYELOPOIESIS

Macrophages are the first myeloid cells seen in the developing embryo. Macrophages are produced along with erythroid progenitors during the primitive wave of hematopoiesis. Neutrophils are first observed during the 5th week of postconception life. Both macrophages and neutrophils arise from a common myeloid progenitor. Granulocyte colony-stimulating factors (G-CSF) and macrophage colony-stimulating factors (M-CSF) have also been detected at 6 weeks of gestation and are expressed by the fetal liver from 8 weeks of gestation.

Fetal blood contains only a few neutrophils till the 3rd trimester due to sterile intrauterine environment. The earliest identifiable progenitor of granulocyte series is a myeloblast. A myeloblast contains large nucleus with prominent nucleoli and

little cytoplasm. The myeloblast undergoes a series of stages over 7–10 days to result in a mature neutrophil (**Fig. 12**). The myeloblast transforms into a promyelocyte with accumulation of primary granules, which are rich in proteins, like myeloperoxidase, cathepsins and defensins. These primary granules are involved in intracellular microbe killing. The promyelocyte then matures into a myelocyte and subsequently a metamyelocyte by accumulation of secondary and tertiary granules respectively (**Table 6**). The metamyelocyte stage loses the capacity to proliferate and matures into a neutrophil. A mature neutrophil circulates in the peripheral blood for 3–12 hours before migrating to the lymphoid tissue where it survives for 2–3 days.

FETAL LYMPHOPOIESIS

The human lymphoid tissue is composed of primary lymphoid organs (thymus and bone marrow) and secondary lymphoid organs (spleen, lymph node, tonsils and Peyer's patches, etc). The primary lymphoid organs develop during the 1st trimester. These lymphoid organs serve as sites of differentiation and maturation of B, T and natural killer (NK) cells from a common lymphoid progenitor.

Table 6 Different types of granules present in myeloid cells

Granules	Cells in which these are present	Content
1°	Granulocytes and monocytes	Myeloperoxidase, defensins, cathepsins, neutrophil elastase
2°	Neutrophils, eosinophils, basophils	Lactoferrin, transcobalamin I, neutrophil collagenase and gelatinase, NGAL
3°	Neutrophils	Gelatinase

Abbreviation: NGAL, neutrophil gelatinase-associated lipocalin.

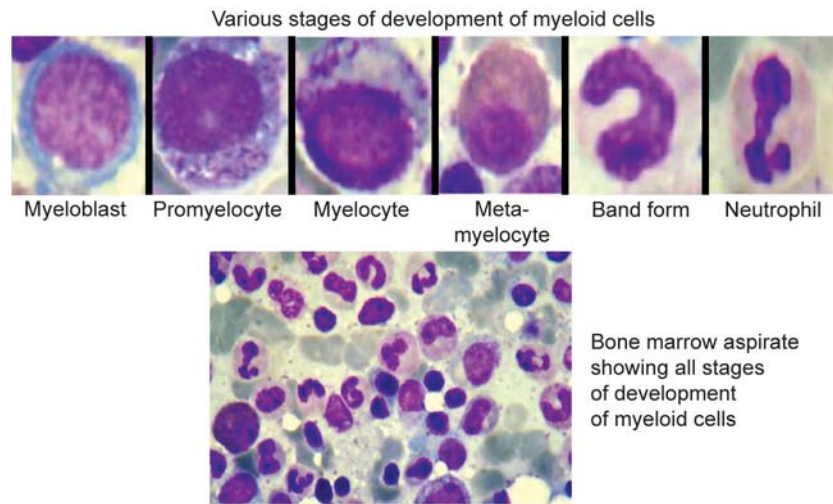


Figure 12 Myelopoiesis

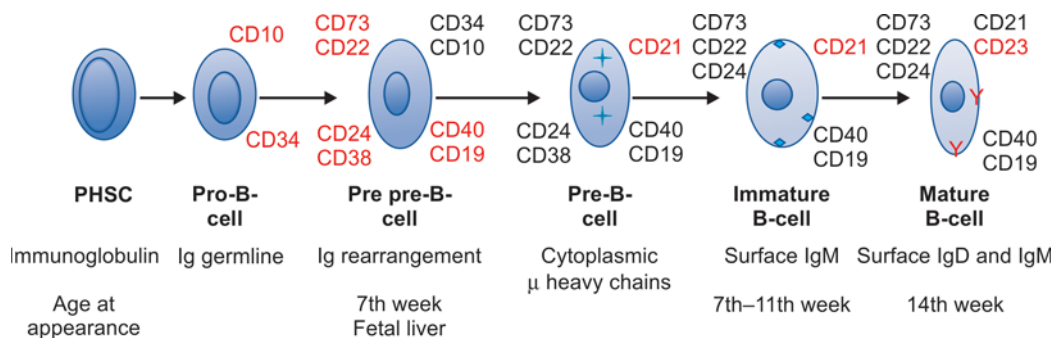


Figure 13 B-cell development; The CD markers in red denote the new ones acquired during development at each stage

Abbreviations: CD, cluster of differentiation; Ig, immunoglobulin.

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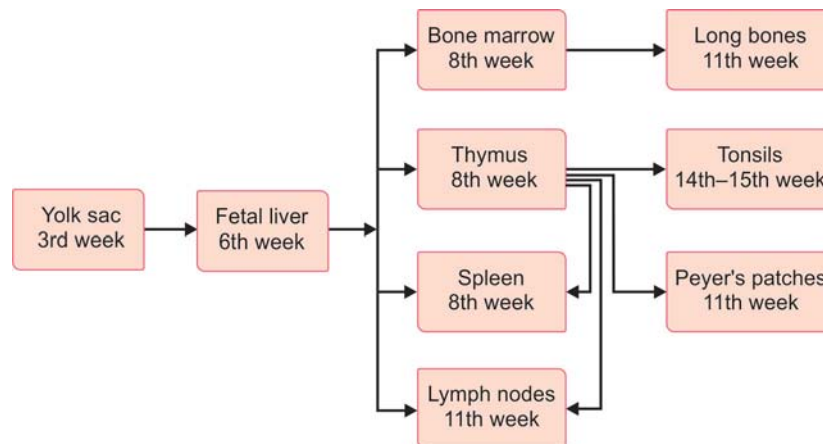


Figure 14 Development of primary and secondary lymphoid organs

B-cells

B-cell development begins in the fetus at about 7 weeks of gestation. The omentum and fetal liver are the main sites of B-cell development. B-cells undergo maturation in two phases: an antigen independent and another antigen-dependent one to form antibody-secreting plasma cells. The development in the antigen independent phase is described in **Figure 13**, the precursor B-cells

undergo immunoglobulin gene rearrangement and acquire new surface markers as they form mature B-cells. During the antigen-dependent phase, the mature B-cells are exposed to a wide array of antigens. The mature B-cells differentiate into a memory cell and an antibody-secreting plasma cell. The development of various primary and secondary lymphoid organs is shown in **Figure 14**.

T-cells

The common lymphoid progenitor in the fetal liver migrates to the thymus probably under the effect of a chemotactic factor. Pro-T-cells bearing surface CD-7 and CD-34 have been detected in fetal liver by 7th week of gestation. Between 8 weeks and 10 weeks of gestation, these pro-T-cells move to thymus and acquire surface T-cell receptors (TCRs) to become pre-T-cells. Human thymic tissue is derived from the 3rd branchial pouch around 4th week of gestation and differentiates into subcapsular, cortical and medullary regions between 9 weeks and 15 weeks of gestation.

The precursor T-cells colonizing the thymus undergo intra-thymic maturation by the process of positive and negative selection from the 2nd trimester onwards till 1–2 years of postnatal life.

The T-cells interact with the major histocompatibility antigens present on the cortical thymocytes via TCRs present on their surface. The T-cells after interaction with these antigens develop the capability to identify the foreign antigens and mature (*positive selection*). Mature T-cells express on their surface either CD-4 or CD-8 receptor which interact with human leukocyte antigen (HLA) class II and class I antigens respectively. The T-cells bearing TCRs capable of interacting with self-antigens undergo programmed cell death (*negative selection*).

Natural Killer Cells

The NK cells are the large granular lymphocytes capable of interacting with the major histocompatibility complex (MHC) antigens and act against various tumors and viruses. NK cells have been detected by 6th week of postnatal life.

ROLE OF CYTOKINES AND GROWTH FACTORS IN HEMATOPOIESIS

The fate of the HSCs depends on various proteins which act on various stages of development. These are called cytokines. Hematopoietic growth factors send out different signals, like proliferation, maturation, differentiation and self-renewal. The actions of various cytokines are described in **Table 7**.

IN A NUTSHELL

1. Hematopoiesis begins in the human as early as 3rd week of gestation. The hematopoietic system is derived from mesodermal cell aggregates in extraembryonic yolk sac.
2. All the cellular components of hematopoietic system are derived from a pluripotent HSC.
3. The site of hematopoiesis shifts sequentially from yolk sac to AGM region to liver, before finally settling in the bone marrow. The change in site of hematopoiesis is accompanied by switch in hemoglobin chains.
4. Stem cell niche provides the optimal microenvironment for the growth and differentiation of hematopoietic stem cells.
5. The MCV and MCH decreases with the gestation age. MCHC remains constant.
6. The platelet production begins by 5th week of gestation. The earliest committed cell is a burst forming unit MK.
7. The platelet production occurs in following steps: production of thrombopoietic factor, proliferation of MK precursors, maturation of MKs and release of platelets.
8. Macrophages are the first cells of the myeloid series to be produced during development followed by neutrophils. Both are derived from a common myeloid progenitor.
9. The development of B-cells begins in the omentum and liver by 7th week of gestation. T-cells mature in the thymus by positive and negative selection from 2nd trimester to 1–2 years of life.
10. The hematopoiesis is regulated by different growth factors and transcription factors which are outside the marrow.

Table 7 Role of cytokines and hematopoietic growth factors in hematopoiesis

IL-1	Induces production of other cytokines from many cells
IL-2	T-cell growth factor
IL-3	Regulates the stem cell growth
IL-4	Regulates mast cell development
IL-5	Eosinophil growth factor
IL-6	Stimulates B-lymphocyte growth
IL-7	Principal regulator of B- and T-lymphocyte growth
IL-8	Promotes survival of cells in response to hematopoietic cytokines
IL-9	Produced by Th-2 lymphocytes Promotes growth of myeloid cells
IL-11	Shares activities with IL-6 increases platelet count in patients with chemotherapy induced thrombocytopenia
IL-15	Stimulates NK cell proliferation
IL-21	Affects growth and maturation of B-, T-, and NK-cells
SCF	Affects primitive hematopoietic cells of all lineages
EPO	Stimulates the proliferation of erythroid progenitors
M-CSF	Promotes the proliferation of monocytic progenitors
G-CSF	Stimulates growth of neutrophilic progenitors
GM-CSF	Affects granulocyte and macrophage progenitors and activates macrophages
TPO	Affects hematopoietic stem cells and megakaryocytic progenitors

Abbreviations: IL, interleukin; NK, natural killer; GM-CSF, granulocyte-macrophage colony-stimulating factor; TPO, thrombopoietin; EPO, erythropoietin.

MORE ON THIS TOPIC

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Chapter 38.2

Approach to Diagnosis of Anemia

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Anemia refers to reduction in the oxygen carrying capacity of blood, as observed by reduced levels of hemoglobin (Hb) concentration and red cell mass [hematocrit (HCT)] leading to tissue hypoxia. For practical purpose, anemia is defined as red blood cell (RBC) mass or Hb measurement less than 2 SD below the mean for normal population. Age appropriate cut-off levels of Hb and blood indices are shown in **Table 1**.

Table 1 WHO cut-off values for diagnosis of anemia

Age/Sex group	Hb (g/dL)
6 months–6 years	< 11
6–14 years	< 12
Adult males	< 13
Adult females (nonpregnant)	< 12
Adult females (pregnant)	< 11

The average life span of RBCs is between 100 days and 120 days. The aged cells are removed from circulation by the reticuloendothelial system, particularly in the splenic pulp where the flow of blood is slow. The cells destroyed each day are replaced by new cells released from marrow, with the result the red cell population in the blood consists of cells ranging in the age from 1 day to 120 days. Approximately 1% of the red cells are destroyed and replaced each day. Any congenital or acquired imbalance in erythrocyte loss relative to the marrow's capacity for erythrocyte production—such as reduced production or increased destruction—leads to anemia.

POINTERS FOR ANEMIA

Growth retardation There is a marked reduction in weight in iron deficient children though height seems to be unaffected.

Exercise intolerance Maximum work capacity, work output and endurance are impaired in iron deficiency state.

Behavioral changes Reduced attention span, irritability, decreased scholastic performance, poor academic achievement and conduct disorders occur in these iron deficient children. Child is usually irritable, resentful, crying excessively, holds breath and throws temper tantrums. The cognitive function also suffers in iron deficient children, at times permanently demonstrated impairment of cognitive function in iron deficient children and significant improvement in Mental Development Index (MDI) and Psychomotor Development Index (PDI) after iron therapy have been reported.

Altered host response Iron deficiency affects both cell mediated as well as humoral immunity. However, oral iron therapy only minimally changes saturation of transferrin and hence practically it does not have any adverse effect on incidence of infection.

APPROACH TO A CHILD WITH ANEMIA

It is pertinent to answer three basic questions while approaching a child with suspected anemia. Is the child anemic? What is the cause of anemia? What is the type of anemia?

Is the Child Anemic?

Lower limit of Hb in the newborn period is 13–14 g/dL; at 3 months, 9 g/dL; 6 months to 6 years, 11 g/dL; and 7–12 years, 12 g/dL. A Hb of 9 g/dL is thus normal for a 3 months old infant and needs no treatment; the same level in a older child may call for hematinic therapy. Hence age appropriate cut-off levels are important to interpret the Hb levels. **Table 2** categorizes the severity of anemia according to Hb levels.

Table 2 Grades of severity of anemia

Grades of anemia severity	Hb%
Mild	10 g% And < normal for the age
Moderate	Between 7 g/dL and 10 g/dL
Severe	Below 7 g/dL and > 5 g/dL
Very severe	< 5 g/dL

Clinical Presentation

The common signs and symptoms of anemia are pallor, tiredness, lassitude, easy fatigability, weakness, and shortness of breath. However, these symptoms are nonspecific and can also be seen in various other conditions including a respiratory illnesses, congestive cardiac failure, renal diseases, or myxedema. Pallor (**Figs 1A and B**) is the most common sign of anemia. The color of skin not only depends upon the Hb content of blood but also on the state of blood vessels in the skin, amount of fluid in the subcutaneous tissue and on the degree of skin pigmentation, associated jaundice and cyanosis and hence pallor out of proportion to actual anemia may be noticed in nephrotic syndrome, renal disorders, hypoproteinemia, and congestive cardiac failure. In simple vasovagal syncope, pallor results from cutaneous vasoconstriction and is not a sign of anemia. Hence it is always prudent to rely on hemoglobin or hematocrit estimation to detect anemia.

What is the Cause and Type of Anemia?

Anemia can be caused due to blood loss; due to decreased (inadequate) production; or due to increased destruction. Detailed history, thorough head to toe examination, screening laboratory tests and confirmatory tests are required in a stepwise approach to establish the etiology of anemia.

Anemia can be typed based on the etiology or the morphology of the red cells. These classifications are discussed in the next chapter. A peripheral blood smear and complete blood counts are



Figures 1A and B Pallor: pale tongue and pale nails. Most common sign of anemia

essential to understand the nature of anemia. Though arriving at a correct diagnosis is important before starting any therapy, doing battery of tests is neither possible nor desirable or cost effective in every case of anemia. Interpretation of laboratory findings for typing of anemia is discussed later in this chapter.

HISTORY TAKING FOR ANEMIA

Time Taken to Develop Anemia

Symptoms depend upon not only upon severity of anemia but also time taken to develop anemia (rate of drop in Hb).

Acute Anemia

Acute anemia at any age usually suggests the possibility of acute external or internal *hemorrhage*; or *hemolysis*. Acute hemolysis usually occurs due to red cell enzyme deficiency or immune destruction. Presence of significant icterus may suggest hemolysis or internal hemorrhage as the cause of anemia. There is no icterus in children with obvious external hemorrhage such as a gastrointestinal (GI) bleed, bleeding following vitamin K deficiency or coagulation factor deficiency or platelet disorder. Child may present with signs of congestive cardiac failure, breathlessness, and restlessness.

Chronic Anemia

Chronic blood loss can be either obvious (recurrent hematemesis) or occult (occult blood in stools). Children may remain asymptomatic for long duration if the onset of anemia is insidious. Child with chronic anemia may be brought walking, with minimal symptoms, even though Hb level may be as low as 3–6 g/dL. In mild anemia there may be no signs and symptoms but a definite sense of well-being and better exercise tolerance is observed following treatment. In severe deficiency, all the symptoms of anemia like fatigue, breathlessness, irritability, anorexia, etc. may be seen. Spleen maybe enlarged, depending on the cause. Depletion of nonheme iron contained in tissue proteins is responsible for various other manifestations.

Age-Specific Causes of Anemia

Newborn Period

Common causes of anemia in the newborn include neonatal blood loss, fetomaternal hemorrhage, and hemolytic disorders. In about 50% of all pregnancies there is some degree of fetomaternal hemorrhage of which 8% are significant (0.5–40 mL fetal blood loss) and 1% severe (> 100 mL fetal blood loss). Approach to neonatal anemia is shown in **Flow chart 1**. It has been discussed in detail in an earlier chapter in the Section on High-risk Newborns.

Anemia in Childhood

Nutritional anemias are usually seen between 6 months and 3 years of age. Alpha thalassemia presents with anemia or hydrops in utero or just after birth. Beta thalassemia usually presents after 6 months of age when fetal hemoglobin (HbF) starts decreasing. A congenital bone marrow hypoplasia will present at or soon after birth.

Family History

G6PD deficiency is more common in *Parsis* and *Sindhis*. Thalassemia is seen more in *Punjabis* and *Sindhis*. Sickle cell anemia (HbS) is more common in Madhya Pradesh and Andhra Pradesh. Family history of *blood transfusions* indicates an inherited cause such as thalassemia, enzyme defects (G6PD deficiency), or membrane defects (hereditary spherocytosis). *Repeated history of blood transfusions* usually indicates a non-nutritional anemia such as hemoglobinopathy, thalassemia, or bone marrow hypofunction.

Pedigree chart including the expired members should be charted meticulously including two generations on each side. Many hemolytic anemias are genetically determined. Certain inherited causes of anemia are transmitted in an X-linked fashion and hence are commonly seen in male children, e.g., G6PD deficiency, phosphoglycerate kinase deficiency. Hereditary spherocytosis are transmitted in an autosomal dominant manner.

Hemoglobinopathies like thalassemia, HbS, etc. are autosomal recessive. A history of consanguineous marriage is also helpful in recessive conditions. A family history of neonatal hyperbilirubinaemia, anemia, jaundice, splenomegaly, splenectomy or gallstones should be asked.

Dietary History

A child with predominantly milk-based diet with minimal or no complimentary feeding is more likely to suffer from nutritional anemia. History of pica suggests an iron deficiency anemia. A child on goat's milk is predisposed to folic acid deficiency due to its poor folate content. Breastmilk, the primary source of infant nutrition is poor in iron, containing 0.28–0.73 mg/L. However, the iron in breastmilk has a very high bioavailability (20–80%) and hence iron deficiency rarely occurs in exclusively breastfed infants till the age of 4–6 months. Breastmilk does not protect against iron deficiency after the age of 6 months unless iron containing weaning foods are introduced.

Iron deficiency in older infants and children occurs due to inadequate dietary intake. Anemia is associated with poor dietary intake of iron, folic acid, B₁₂, proteins and Vitamin E and C in the diet. Non-introduction of iron containing weaning foods or continuation of only milk feeds leads to iron-deficiency anemia (IDA) in infants. Food fads may be responsible for anemia in adolescent period. During adolescence, false concerns about the body figure, food fads, ignorance, particularly in girls lead to iron deficiency.

History of Bleeding

History of skin bleeds (petechiae or ecchymosis) or *bleeding from any other sites* suggests platelets or a hepatic involvement. Chronic liver disease could be a cause of anemia that will also affect the coagulation factors and lead to bleeding manifestations. Skin bleeds associated with anemia suggests hypoplasia or infiltration of the bone marrow. The chronic loss of few milliliters of blood daily is sufficient to deplete iron stores and leads to iron deficiency. Stool examination for occult blood is helpful. Trauma, GI bleeding, chronic occult blood loss often occurs in inflammatory bowel disease, Meckel diverticulum, parasitic infestation particularly hookworm infestation are important cause of intestinal blood.

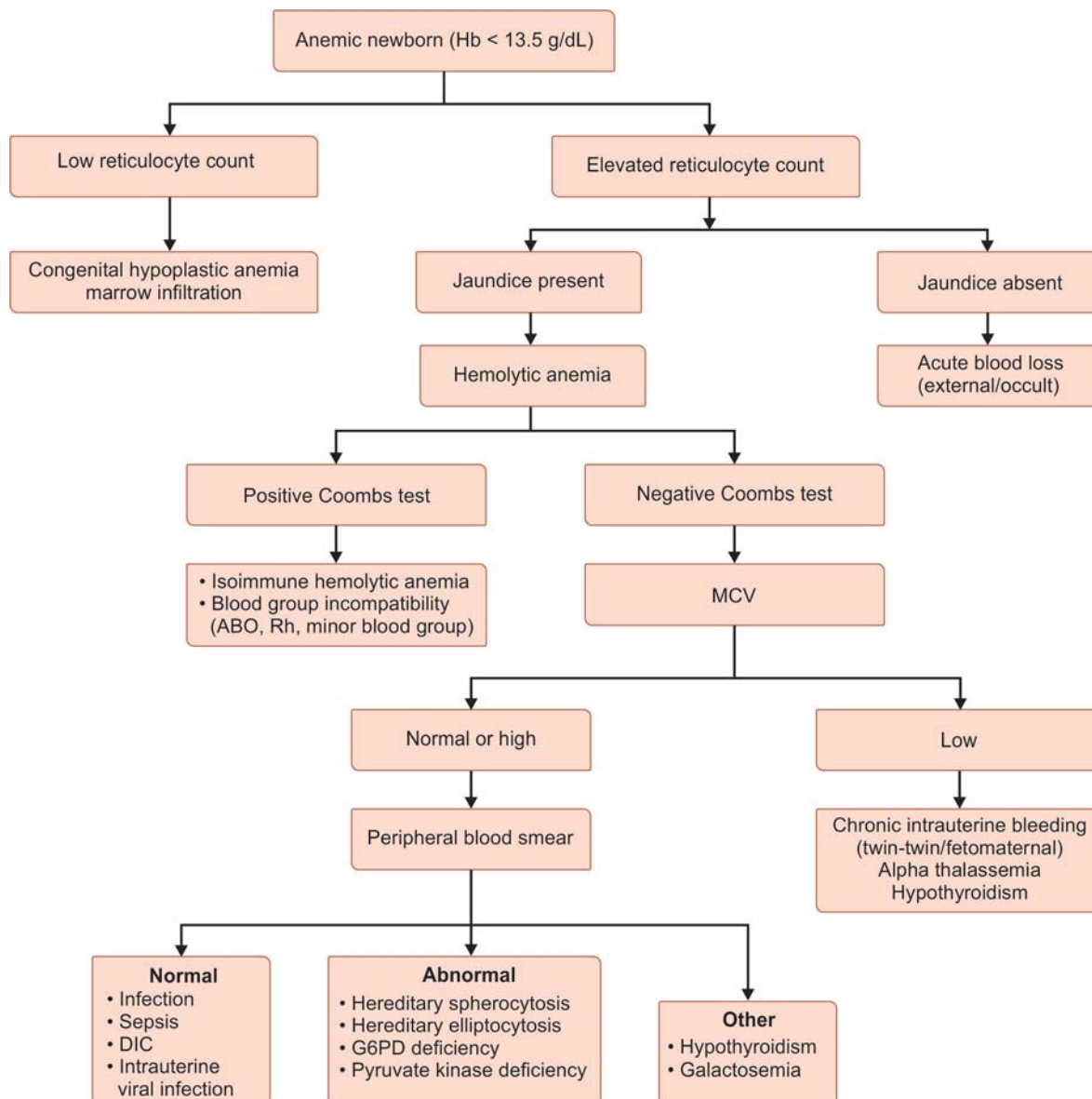
History of Drug Ingestion

Certain drugs can lead to decreased production due to hypoplasia or aplasia of the bone marrow, e.g., chloramphenicol, salicylates, analgesics and nonsteroidal anti-inflammatory drug (NSAID) group of drugs. Some drugs can lead to increased destruction of the RBCs, as is seen in drug-induced hemolytic anemias (penicillin and cephalosporin group, alpha-methyldopa, stibophen, etc.).

Anti-infective drugs like sulfa drugs, nalidixic acid, nitrofurantoin, antimalarials like primaquine, quinine, mefloquine, furazolidone, can lead to hemolysis in individuals with G6PD deficiency. Drugs can also produce megaloblastic anemia, e.g., phenytoin, folate antagonists, etc.

History of Infections

History of fever with sudden appearance of pallor suggests malaria. Bacterial or viral infection leading to cytokine-mediated decrease in iron utilization and RBC production—anemia of chronic infection.

Flow chart 1 Approach to anemia in neonates

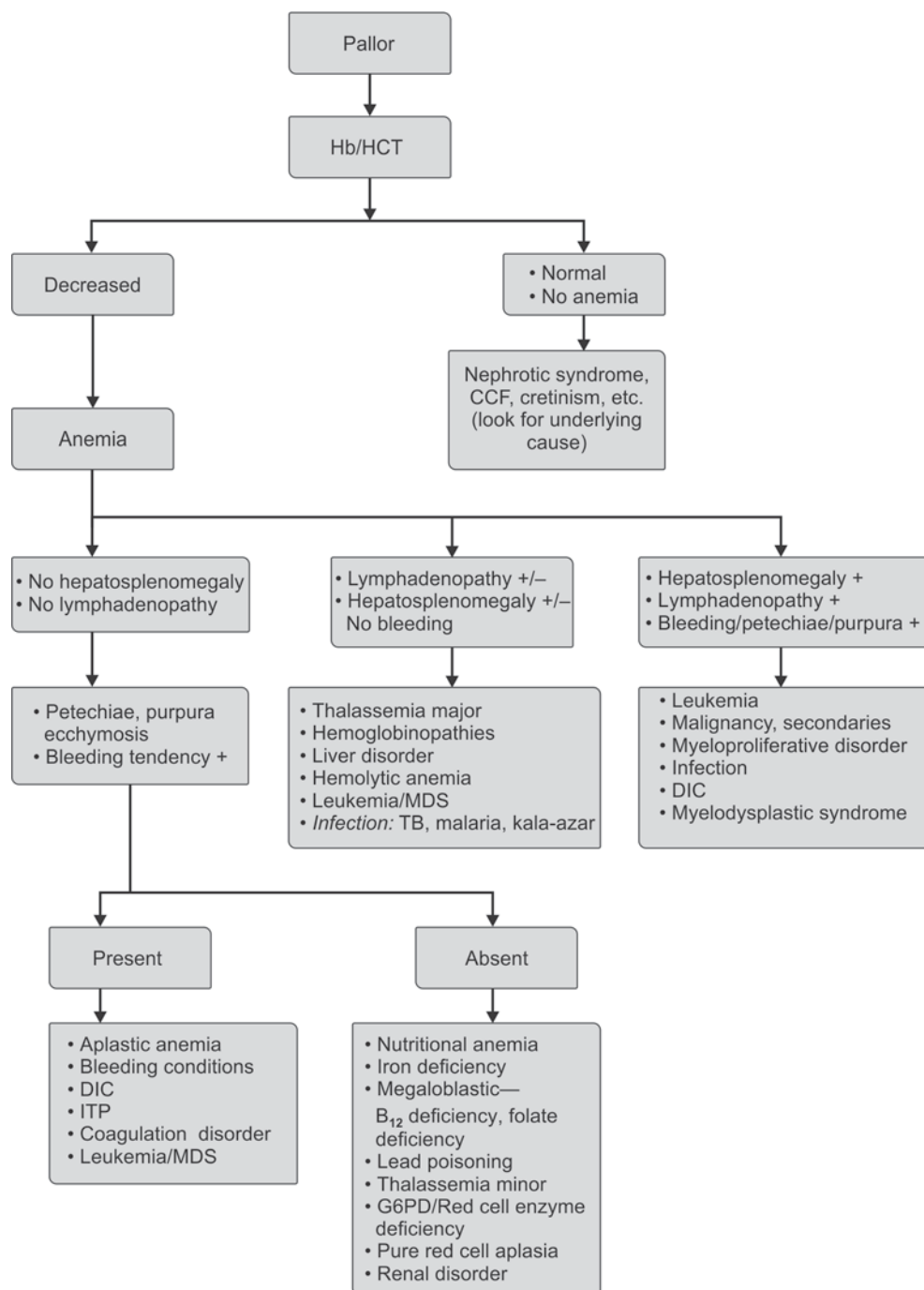
PHYSICAL EXAMINATION

Some physical signs help clinch the diagnosis. To ascertain severity, pulse, blood pressure and respiratory rate should be recorded. Look for puffiness, edema feet, sacral edema, jugulovenous pulse, tenderness, hepatojugular reflux and basal crepitations. All these will help to diagnose congestive cardiac failure as, such children need urgent treatment. Hypertension may be seen in anemia due to renal diseases. Clinical approach to anemia is shown in **Flow chart 2**.

Facies

Hemolytic facies (**Fig. 2**) will have frontal and parietal bossing, large head, depressed bridge of nose, malar prominence, sallow complexion, irregular maxillary teeth with anterior overbite. Hypothyroidism will have typical cretin facies and may be missed. Hemolytic facies suggests chronic hemolysis and extramedullary hematopoiesis as in thalassemia major. This can be confirmed by hair on end appearance in X-ray of the skull (**Fig. 3**).

**Figure 2** Hemolytic facies

Flow chart 2 Clinical approach to anemia

Abbreviations: Hct, hematocrit; CCF, congestive cardiac failure; DIC, disseminated intravascular coagulation; MDS, myelodysplastic syndrome.

Diamond-Blackfan syndrome (DBA) (Figs 4A and B) is characterized by box like face, high arched palate, and triphalangeal thumb. Diagnosis is confirmed by bone marrow examination which shows conspicuous absence of red cell precursors. They have persistent low retic count, macrocytosis, elevated fetal Hb1 antigen and elevated adenosine deaminase levels in the RBCs and usually diagnosed in early infancy in the first 2 years of life.

Eyes Fanconi anemia will have microcornea. Conjunctival vessels tortuosity is seen in HbS and so is the presence of retinal hemorrhage or microaneurysms. Presence of mild jaundice without passage of

high colored urine indicates a process of hemolysis. Osteopetrosis child will develop blindness as time passes by.

Oral cavity Look for glossitis, angular stomatitis, bald tongue which will suggest nutritional anemia. Look for teeth abnormality for hemolytic anemia.

Nail Changes

Platonychia, koilonychia, brittle nails are suggestive of iron deficiency. They are less common in children than in adults, but when present are pathognomonic of iron deficiency anemia (IDA). Dyskeratotic nails will be seen in dyskeratosis congenita.

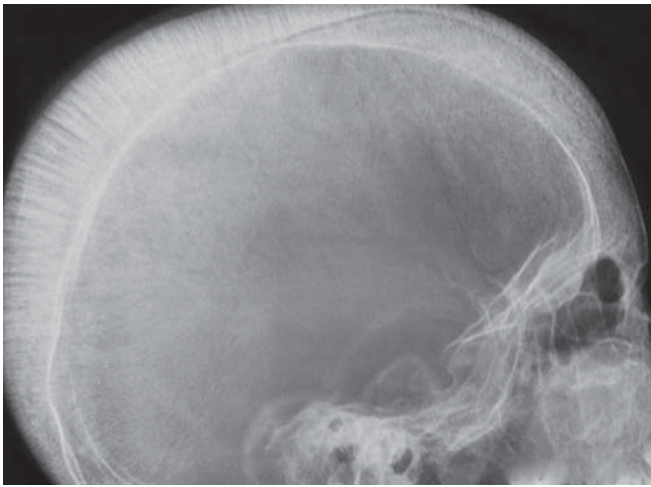


Figure 3 Hair on end appearance in thalassemia

Lymphadenopathy

Significant lymphadenopathy may suggest tuberculosis, HIV, infectious mononucleosis, leukemia, or lymphoma as the cause of anemia.

Hepatosplenomegaly

Presence of significant hepatosplenomegaly with lymphadenopathy is highly suggestive of malignancy (leukemia and lymphoma). Significant hepatosplenomegaly without lymphadenopathy suggests hemolytic anemia, e.g., thalassemia, or infective pathology (malaria). HIV-AIDS should also be ruled out in presence of hepatosplenomegaly. Hepatosplenomegaly with fever and anemia may be suggestive of malaria and kala-azar. Storage disorders should also be considered in a child with hepatosplenomegaly with systemic manifestations. Isolated splenomegaly favors enteric fever, malaria, portal hypertension, lymphoma, chronic myelogenous leukemia (CML), tropical splenomegaly or hypersplenism, immune hemolytic anemia, or congenital spherocytosis as the cause of anemia.

Bleeding Manifestation

Presence of bleeding tendencies with petechiae, purpura will suggest thrombocytopenia which can be seen in benign diseases like immune thrombocytopenic purpura (ITP) or in serious diseases like aplastic anemia, malignancies or marrow infiltration. Child with ITP is usually a well child without fever, hepatosplenomegaly,

lymphadenopathy, weight loss or bony tenderness as compared to a child with bone marrow failure or leukemia who will be a sick child with fever, weight loss, bony tenderness, lymphadenopathy and hepatosplenomegaly.

Mucosal Changes

Glossitis, angular stomatitis and bald tongue are rarely seen in deficiency of B₁₂, folic acid and iron in small children. Atrophic gastritis and achlorhydria and small bowel changes leading to esophageal mucosal web as seen in Plummer-Vilson syndrome, also called Paterson-Kelly syndrome are rare in children and are more common in adolescent and adults with nutritional anemia.

Skeletal Changes

Childs with Fanconi anemia and thrombocytopenia-absent radius (TAR) syndrome, etc. have skeletal malformations like absent radius, absent or bifid thumb, triphalangeal thumb, polydactyly, syndactyly, short stature, microcephaly. Look for associated anomalies like mental retardation, skin hyperpigmentation, hypogonadism, and renal anomalies (**Figs 5A and B**).

Skin Changes

Hyperpigmentation is seen in Fanconi anemia. Icterus is seen in liver diseases as well as hemolytic anemia. Nonhealing ulcers over lower limbs are seen in any chronic hemolytic anemia especially in HbS and hemoglobin C (HbC) disease (**Fig. 6**). Disseminated intravascular coagulation (DIC) like picture with anemia and thrombocytopenia in a child with giant cavernous hemangioma suggests Kasabach-Merritt syndrome (**Fig. 7**).

Kasabach-Merritt Syndrome

Also known as hemangioma with thrombocytopenia, this disorder was first described in 1940. It is a rare disease usually of infants in which vascular tumor leads to decreased platelet count often presenting at birth. It is usually caused by hemangioendothelioma or other vascular tumor. The condition may progress to disseminated intravascular coagulation. Microangiopathic hemolytic anemia of RBC is often associated. Peripheral smear reveals helmet cells, broken cells, crenated RBCs. Tumors may be found over the trunk upper and lower extremities, retroperitoneum and in the cervical and fascial area.

LABORATORY APPROACH TO CHILDHOOD ANEMIA

Though arriving at a correct diagnosis is very important before starting any therapy, doing battery of tests is neither possible



Figures 4A and B (A) Diamond-Blackfan syndrome (DBA); (B) Bone marrow showing absence of normoblasts in BM



Figures 5A and B Skeletal changes in Fanconi anemia. (A) Absent radius; (B) Bifid thumb, hyperpigmentation, hypogonadism, renal anomalies in such cases



Figure 6 Nonhealing ulcers in sickle cell anemia (HbS) disease

nor desirable or cost effective in every case of anemia. Hence the investigations needed to be done are classified into two categories viz. screening tests and confirmatory tests.



Figure 7 Kasabach-Merritt syndrome

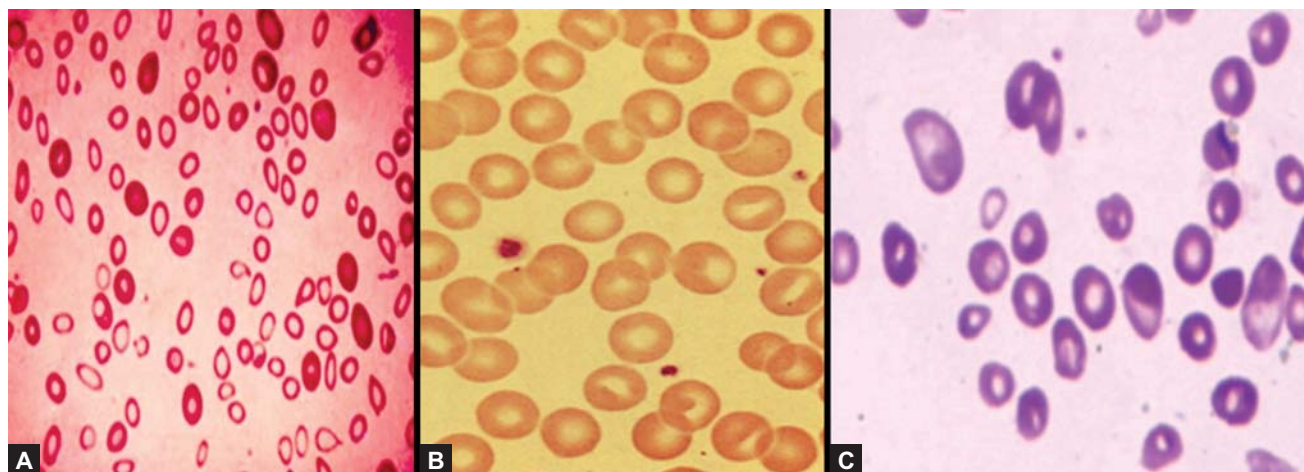
Screening Tests

These include Hb, complete blood count, reticulocyte count, HCT, blood indices, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC) and red cell width (RDW) and thorough examination of peripheral smear which must be done in all cases for diagnosing anemia. It not only suggests the type of anemia but also gives the clue to the underlying disease and indicates specialized investigations needed further, thus minimising the number of tests and expenses. It also gives direction for further management.

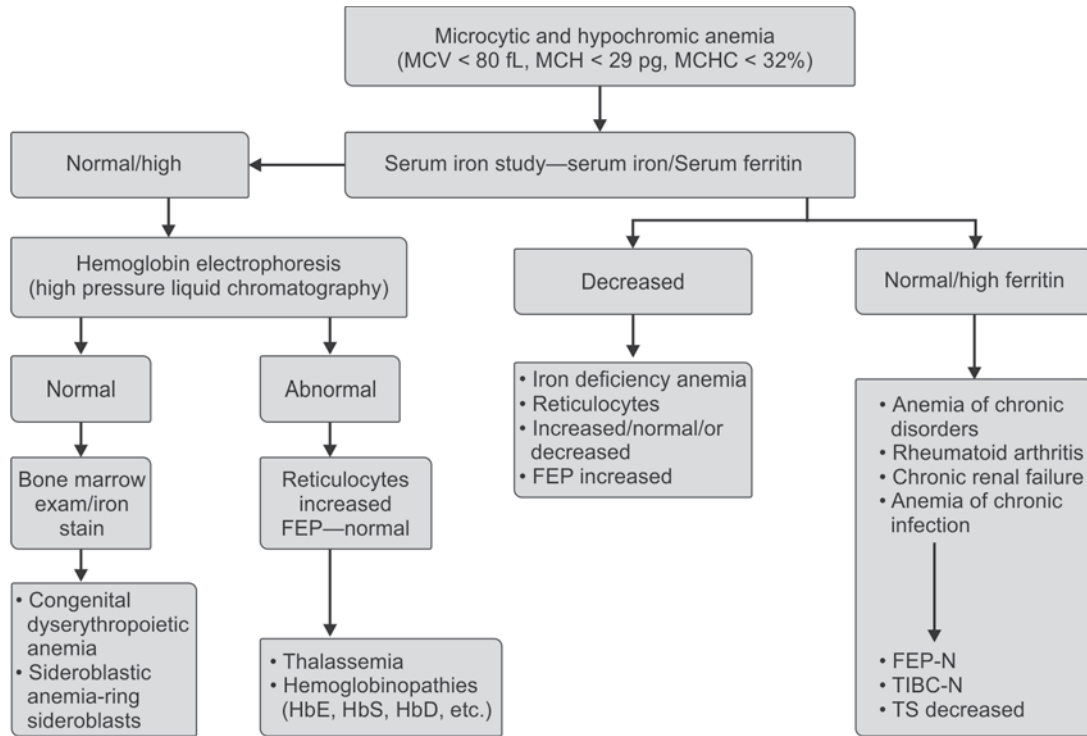
Peripheral smear examination should be done on fresh smears taken from finger prick. It is ideally done on particle cell counter which gives accurate and reproducible results as compared to manual methods. Based on erythrocyte size anemia is further classified as microcytic, normocytic and macrocytic (**Figs 8A to C**). Approach to anemia based upon morphologic classification is provided in **Flow charts 3 to 5**. For details refer to the next chapter on classification on anemia.

Red Cell Width

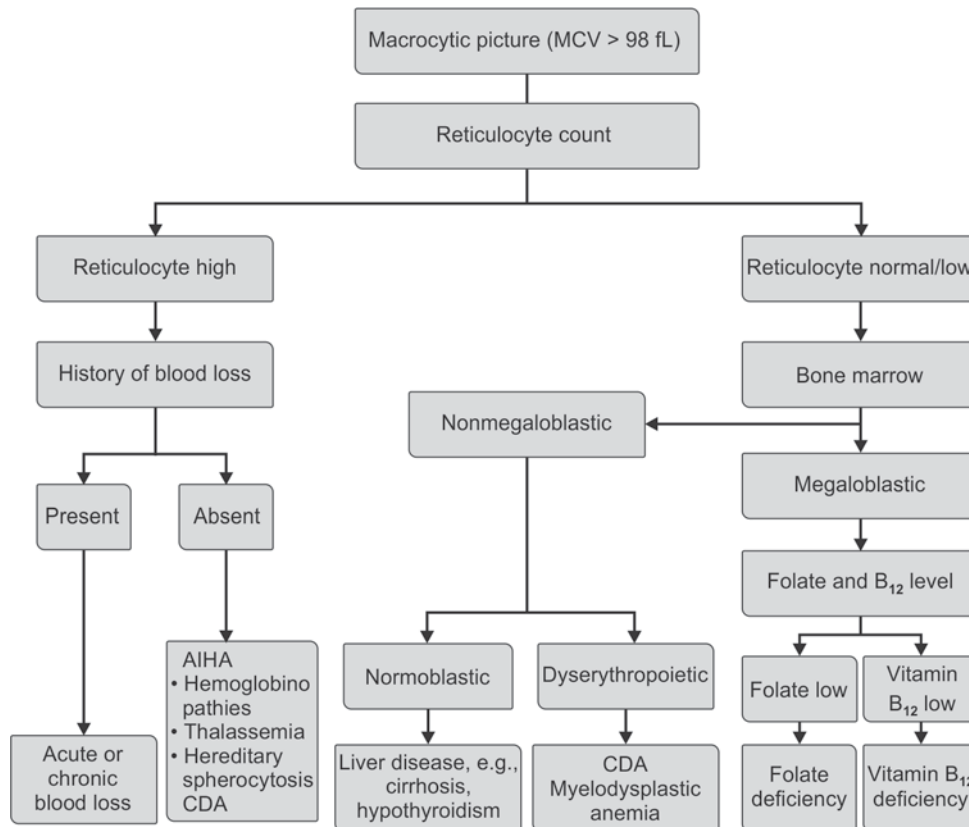
Red cell width indicates the variation in RBC size. Increased RDW indicates presence of anisocytosis as seen in iron deficiency anemia and a normal value (12–14) indicates not much variation in size of the RBCs as in thalassemia.



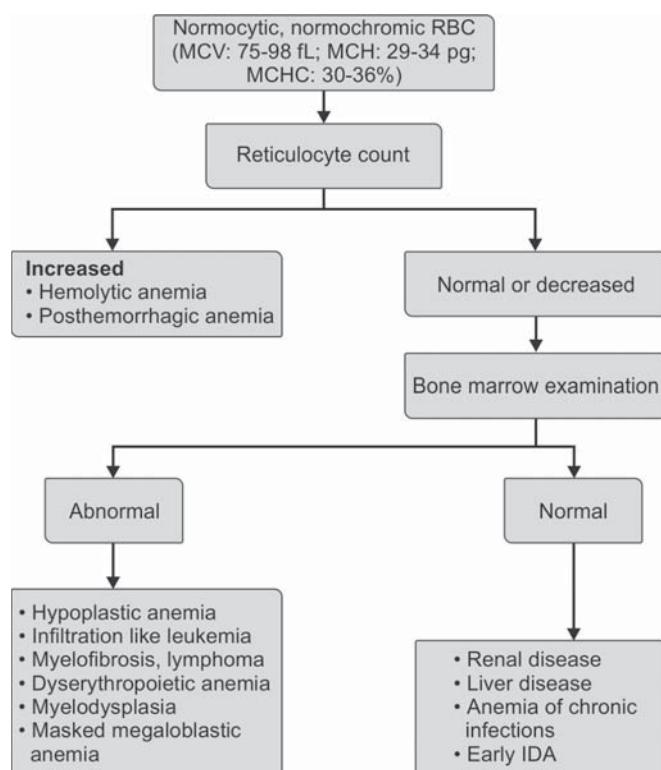
Figures 8A to C (A) Microcytic anemia; (B) Normocytic anemia; and (C) Macrocytic anemia

Flow chart 3 Microcytic and hypochromic picture on peripheral blood smear

Abbreviations: MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; FEP, free erythrocyte protoporphyrins; TIBC, total iron-binding capacity.

Flow chart 4 Macrocytic picture on peripheral blood smear

Abbreviations: MCV, mean corpuscular volume; AIHA, autoimmune hemolytic anemia; CDA, congenital dyserythropoietic anemias.

Flow chart 5 Normocytic, normochromic anemia**Reticulocyte Count**

Number of reticulocytes in the blood reflects the bone marrow activity and is expressed as the percentage of the total RBC count. If the bone marrow is hyperactive as in cases of hemolytic anemia, the reticulocyte count increases. The reticulocyte count is decreased in patients with bone marrow hypoplasia or aplasia.

Anemia per se results in increased bone marrow activity to compensate for decreased Hb, leading to falsely high reticulocyte count. Therefore, correction should be made for the existing severity of anemia. This is done as follows:

$$\text{Corrected reticulocyte count} = \frac{\text{Actual reticulocyte count} \times \text{Packed cell volume (PCV)}}{0.45 \text{ (normal PCV)}}$$

Bone Marrow

Bone marrow examination is very helpful in making a diagnosis as many times the peripheral blood examination may not reveal the true picture. A peripheral pancytopenia may not be associated with

bone marrow aplasia suggesting an alternate diagnosis. Similarly a peripheral macrocytic picture may not be associated with megaloblastosis in bone marrow suggesting towards a diagnosis other than vitamin B₁₂ or folic acid deficiency. Bone marrow examination can be diagnostic in aplastic anemia and leukemia. Bone marrow examination will show hyperplasia in patients with hemolytic syndrome and hypersplenism.

Special Investigations

Specific investigations for etiological diagnosis include serum iron studies, serum folate and vitamin B₁₂ levels for deficiency anemias; and Hb electrophoresis for hemoglobinopathies and thalassemia.

IN A NUTSHELL

1. Detailed history, clinical examination and complete blood counts along with a peripheral blood smear examination and various algorithms aid in reaching a diagnosis.
2. Detailed peripheral smear examination is of utmost importance. Its examination not only helps in classification of anemia but presence of other red cell abnormalities, gives clue to the underlying diagnosis.
3. These children may be subjected to few additional, specific tests for confirmation of etiology of anemia.

MORE ON THIS TOPIC

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Chapter 38.3

Anemia: Etiology and Classification

Nitin Shah, Sunil Udgire

When faced with a child with anemia, one needs to establish the severity of anemia for immediate action, type of anemia to ask for necessary diagnostic tests and identify the etiology of anemia to understand the basis behind. This section will help you understand these principles.

HISTORICAL ASPECTS

Anemia was described as pallor, breathlessness and edema in about 1500 BC in Papyrus Ebers, an Egyptian manual of therapeutics, which is believed to be the first complete description of iron deficiency. Pernicious anemia was described by Thomas Addison in 1855 which also suggested role of cobalamin deficiency as the cause. Subsequently in 1880 Ehrlich described the term megaloblast for the abnormal normoblast seen in megaloblastic anemia. Cooley described what is now known as thalassemia in 1925. First case of thalassemia from India was probably reported in 1938 from Calcutta. Sydenstricker described the first case of sickle-cell anemia in children and the first case of sickle-cell disease in an Indian immigrant was reported from Cape Town by Berye and Bull in 1943 and from within India by Lehmann and Catbush in 1952 among Veddoids aboriginal tribes of Nilgiri Hills in South India.

EPIDEMIOLOGY

Anemia is a global public health problem affecting both developing and developed countries with major consequences for human health as well as social and economic development. According to an estimate carried out between 1993 and 2005 by World Health Organization (WHO), prevalence of anemia in preschool aged children was 47.4% and school aged children 25.4%, while that of preschool children from South-East Asia as per WHO-region was 65.5%.

Iron deficiency is the most common and widespread nutritional disorder in the world. In nonmalaria endemic regions, 60% of cases of anemia are due to iron-deficiency anemia (IDA). For malaria endemic regions, approximately 50% of anemia is attributable to iron deficiency. In India prevalence of IDA in children was estimated to be 70% in 1990 by Chakraborty and not much has changed in recent time as studies done since 2000 show prevalence of 60–90% at different age in children. Modern *zero figure trends* and the resultant increase in the followers of vegan diet have led to a surge in the number of anemia cases in the Western world too. Over the last few decades, cobalamin and folic acid deficiency have emerged as equally big problems.

According to WHO, about 5% of the world population is carrier for different inherited disorders of hemoglobin (Hb) and about 370,000 severely affected homozygote or compound heterozygote cases of thalassemia are born every year. The United Nations Children's Fund (UNICEF) in 1996 estimated that there were 29.7 million carriers of beta-thalassemia trait in India and about 10,000 infants with homozygous beta-thalassemia born every year. The general incidence of thalassemia trait and sickle-cell hemoglobinopathies in India varies between 3–17% and 1–44% respectively. It is estimated that there are about 65,000–67,000 beta-thalassemia patients in India with around 9,000–10,000 cases being added every year. The carrier rate for beta-thalassemia gene varies from 1–3% in Southern India to 3–15% in Northern India.

DEFINITION

Derived from the Greek term which means *bloodlessness*, anemia is defined as decreased red blood cell (RBC) volume (reflected by RBC count and Hb concentration per RBC and hematocrit) or reduced Hb concentration below the age-appropriate normal values. Main function of RBCs is to carry oxygen to and carbon dioxide from the tissues. Anemia therefore will lead to tissue hypoxia at cellular levels which is difficult to measure in day-to-day clinical practice. Child is said to be anemic when the Hb and/or hematocrit is two standard deviations below mean for that particular age and sex. The normal Hb levels along with normal red cell values at different ages, i.e., from newborn to adulthood are given in **Table 1**. WHO cut-offs for defining anemia at various ages have been listed in the previous chapter.

CLINICAL MANIFESTATIONS

The manifestations of anemia depend on five factors, viz.: (1) reduction in oxygen-carrying capacity of blood, (2) degree of change in total blood volume, (3) speed at which the previous two factors developed, (4) capacity of the cardiovascular and pulmonary systems to compensate for the anemia and (5) associated manifestations of the underlying disorder that resulted in the development of anemia. Clinical presentation has been covered in the previous chapter on approach to anemia.

ETIOLOGY AND CLASSIFICATION OF ANEMIA

Anemia can be classified on the basis of etiology which helps us understand the pathophysiology of anemia. Morphological classification based on size and shape of red cells helps us investigate a case of anemia and zero down on close differentials. Classification based on severity of anemia helps us decide the plan of management of a case and need of transfusion. A combined approach will help us understand, investigate and manage a case of anemia, especially when the child is sick.

Etiological Classification

There are four basic causes of anemia: (1) decreased production, (2) increased losses in form hemorrhage or (3) hemolysis and (4) sequestration. We can separate the causes of anemia into two broad categories: (1) Disorders of red cell production, in which net red cell production is depressed. This can be due to either ineffective erythropoiesis (disorders of erythroid maturation) or absolute failure of erythropoiesis. (2) Disorders in which rapid destruction of red cells occur due to hemorrhage or hemolysis. In some cases of anemia, more than one mechanism may be involved but one functional disorder is generally the major reason responsible for anemia. Etiological classification of anemia is given in **Table 2**.

Classification Based on Severity and Onset

Anemia can be classified based on severity as per WHO guidelines:

- Mild, when Hb concentrations are above 10 g/dL but below the cut-off value
- Moderate when the concentration is between 7 g/dL and 10 g/dL
- Severe when it is below 7 g/dL.

Anemia can also be classified based on its onset into *acute anemia* which develops over days to weeks and *chronic anemia* which develops over months. This was also discussed in the previous chapter. Severity of anemia along with clinical condition of patient, especially status of compensation, will help clinician make treatment plan. For example, a 2-year-old child with Hb of 3 g/dL due to iron deficiency would have developed anemia over months and hence will be stable and would not need transfusion unless in occult or overt congestive cardiac failure. Whereas in the

Table 1 Red cell values at various ages: mean and lower limit of normal (-2 SD)*

Age	Hemoglobin (g/dL)		Hematocrit (%)		Red cell count ($10^{12}/L$)		MCV (fL)		MCH (pg)		MCHC (g/dL)		Reticulocytes	
	Mean	-2 SD	Mean	-2 SD	Mean	-2 SD	Mean	-2 SD	Mean	-2 SD	Mean	-2 SD	Mean	-2 SD
Birth (cord blood)	16.5	13.5	51	42	4.7	3.9	108	98	34	31	33	30	3.2	1.8
1–3 days (capillary)	18.5	14.5	56	45	5.3	4.0	108	95	34	31	33	29	3.0	1.5
1 week	17.5	13.5	54	42	5.1	3.9	107	88	34	28	33	28	0.5	0.1
2 weeks	16.5	12.5	51	39	4.9	3.6	105	86	34	28	33	28	0.5	0.2
1 month	14.0	10.0	43	31	4.2	3.0	104	85	34	28	33	29	0.8	0.4
2 months	11.5	9.0	35	28	3.8	2.7	96	77	30	26	33	29	1.6	0.9
3–6 months	11.5	9.5	35	29	3.8	3.1	91	74	30	25	33	30	0.7	0.4
0.5–2 years	12.0	10.5	36	33	4.5	3.7	78	70	27	23	33	30	1.0	0.2
2–6 years	12.5	11.5	37	34	4.6	3.9	81	75	27	24	34	31	1.0	0.2
6–12 years	13.5	11.5	40	35	4.6	4.0	86	77	29	25	34	31	1.0	0.2
12–18 years														
Female	14.0	12.0	41	36	4.6	4.1	90	78	30	25	34	31	1.0	0.2
Male	14.5	13.0	43	37	4.9	4.5	88	78	30	25	34	31	1.0	0.2
18–49 years														
Female	14.0	12.0	41	36	4.6	4.0	90	80	30	26	34	31	1.0	0.2
Male	15.5	13.5	47	41	5.2	4.5	90	80	30	26	34	31	1.0	0.2

From: Dallman PR. Blood and blood-forming tissue. In: Rudolph A. Pediatrics. 16th ed. E Norwalk, CT: Appleton-Cernuary-Croles; 1977.

*These data have been compiled from sources. Emphasis is given to studies employing electronic counters and to the selection of populations that are likely to exclude individuals with iron deficiency. The mean \pm 2 SD can be expected to include 95% of the observations in a normal population.

Abbreviations: SD, standard deviation; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration.

same child if the anemia is due to acute hemolysis say following glucose-6-phosphate dehydrogenase (G6PD) deficiency will be grossly sick and will certainly need transfusion. Also in a sick child with severe anemia, which is acute in onset the treatment, gets priority rather than wasting time in elaborate investigations. One can always investigate the child later.

Morphological Classification

This approach helps us narrow down the differential diagnosis and at times even clinches a diagnosis. Anemia is classified morphologically based on red cell indices as well as evaluation of peripheral smear for red cell size, shape and other abnormalities. It shows whether the anemia is microcytic, normocytic, or macrocytic; hypochromic or normochromic; shows specific morphologic abnormalities suggestive of red cell membrane disorders (e.g., spherocytosis, stomatocytosis or elliptocytosis) or hemoglobinopathies (e.g., sickle-cell disease, thalassemia). This classification is also arbitrary, and categories are not mutually exclusive. Classification based on red cell size and reticulocyte count is shown in **Table 3**.

Fully automated techniques are available for determination of Hb, hematocrit and red cell indices to precisely classify anemia. Steps to follow in investigation of anemia are detailed clinical history and physical examination, complete blood examination to determine whether the abnormality is isolated to a single cell line (RBCs only) or whether it is part of a multiple cell line abnormality; determine morphological type of anemia depending on blood smear and red cell indices, mean corpuscular volume (MCV), and red cell volume distribution width (RDW); reticulocyte count

for degree of erythropoiesis; and look for evidence of hemolytic process, clinical and laboratory features. Bessman and associates have provided a classification of anemia based on MCV and RDW. An updated version that includes mean corpuscular hemoglobin concentration (MCHC) is shown in the **Table 4**. Red cell disorders can be classified according to their predominant morphology. An approach to such a classification is presented in **Table 5**.

IN A NUTSHELL

1. Iron deficiency is the most common and widespread nutritional disorder in the world.
2. Anemia can be classified on the basis of etiology which helps us understand the pathophysiology of anemia.
3. Morphological classification based on size and shape of red cells helps us investigate a case of anemia and zero down on close differentials.
4. Classification based on severity of anemia helps us decide the plan of management of a case and need of transfusion.
5. Blood smear is very useful tool in diagnosis of anemia, and it should not be overlooked in busy practice.
6. Steps to follow in investigation of anemia are detailed clinical history and physical examination, complete blood examination, determine morphological type of anemia; reticulocyte count for degree of erythropoiesis; and look for evidence of hemolytic process, clinical and laboratory features.

Table 2 Etiological classification of anemia

I. Impaired red cell production due to deficiency	
<ul style="list-style-type: none"> • <i>Decreased dietary intake:</i> Iron, B₁₂ • <i>Increased demand:</i> Growth (iron), chronic hemolysis (folic acid) • <i>Decreased absorption:</i> Malabsorption, intrinsic factor deficiency (B₁₂) • Iron deficiency • Vitamin B₁₂ deficiency • Folic acid deficiency • Protein malnutrition • Vitamin B₆ deficiency • <i>Impaired erythropoietin production:</i> CRF, hypothyroidism, hypopituitarism 	
II. Impaired red cell production due to bone marrow failure	
<ul style="list-style-type: none"> • <i>Aplastic anemia:</i> Congenital or acquired • <i>Pure red cell aplasia:</i> Congenital (Diamond-Blackfan syndrome), acquired (TEC) • <i>Marrow infiltration:</i> Malignancies, osteopetrosis, myelofibrosis (CRF, vitamin D deficiency) • Pearson syndrome 	
III. Blood loss	
IV. Hemolytic anemia	
<ul style="list-style-type: none"> • Cellular defects: <ul style="list-style-type: none"> – <i>Membrane defects:</i> Spherocytosis, elliptocytosis, stomatocytosis – <i>Enzyme defects:</i> Pyruvate kinase, G6PD deficiency – <i>Hemoglobin defects:</i> Thalassemia syndromes, sickle-cell anemia • Extracellular defects: <ul style="list-style-type: none"> – <i>Autoimmune:</i> Warm, cold antibody – <i>Fragmentation hemolysis:</i> DIC, TTP, HUS, ECMO, prosthetic heart valves, burns – Hypersplenism – <i>Plasma factors:</i> Liver disease, abetalipoproteinemia, infections, Wilson disease 	

Abbreviations: TEC, transient erythroblastopenia of childhood; CRF, chronic renal failure; G6PD, glucose-6-phosphate dehydrogenase; DIC, disseminated intravascular coagulation; TTP, thrombotic thrombocytopenic purpura; HUS, hemolytic-uremic syndrome; ECMO, extracorporeal membrane oxygenation.

Table 3 Classification of anemia based on red cell size

I. Microcytic anemia (MCV low):	
<ul style="list-style-type: none"> • <i>Low or inadequate reticulocyte count</i> <ul style="list-style-type: none"> – Iron deficiency – Thalassemia trait – Chronic disease – Lead poisoning – Copper deficiency – Sideroblastic anemia • <i>High reticulocyte count</i> <ul style="list-style-type: none"> – Thalassemia syndromes – Pyropoikilocytosis – Hemoglobin C and E disease 	
II. Macrocytic anemia (MCV high):	
<ul style="list-style-type: none"> • <i>Low or inadequate reticulocyte count</i> <ul style="list-style-type: none"> – Vitamin B₁₂ deficiency – Folic acid deficiency – Congenital and acquired aplastic anemia – Hypothyroidism – Orotic aciduria – Drug induced • <i>High reticulocyte count</i> <ul style="list-style-type: none"> – Dyserythropoietic anemia type I and III – Active hemolysis 	
III. Normocytic anemia (MCV normal):	
<ul style="list-style-type: none"> • <i>Low or inadequate reticulocyte count</i> <ul style="list-style-type: none"> – Chronic disease – Malignancy – RBC aplasia (TEC) – Renal failure – Endocrinopathies – Hypersplenism – Dyserythropoietic anemia type II – Hemophagocytic anemia • <i>High reticulocyte count</i> <ul style="list-style-type: none"> – <i>Antibody-mediated hemolysis:</i> Warm, cold – <i>Microangiopathy:</i> DIC, HUS, TTP – <i>Membranopathies:</i> Spherocytosis, elliptocytosis – <i>Enzymopathies:</i> Pyruvate kinase, G6PD deficiency – <i>Hemoglobinopathies:</i> HBSS, SC 	

Abbreviations: MCV, mean corpuscular volume; RBC, red blood cell; TEC, transient erythroblastopenia of childhood; DIC, disseminated intravascular coagulation; HUS, hemolytic-uremic syndrome; TTP, thrombotic thrombocytopenic purpura; G6PD, glucose-6-phosphate dehydrogenase.

Table 4 Relationship of MCV and red cell distribution width (RDW) in a variety of red cell disorder

RDW	Mean corpuscular volume (MCV)		
	Low	Normal	High
Normal	Heterozygous α - and β -thalassemia	Normal Lead poisoning Early iron deficiency Liver disease	Aplastic anemia
High	Iron deficiency Hemoglobin H disease S β -thalassemia		Newborns, prematurity Vitamin B ₁₂ deficiency or folate deficiency
		High MCHC	High MCHC
		Immune hemolytic anemia SS and SC disease Hereditary spherocytosis	Immune hemolytic anemia

Adapted from Bessman JD, Gilmer PR, Gardner FH. Improved classification of anemias by MCV and RDW. *Am J Clin Pathol.* 1983;80(3):322-6.

Abbreviations: MCV, mean corpuscular volume; RDW, red cell volume distribution width; MCHC, mean corpuscular hemoglobin concentration; SC, sickle cell.

Table 5 Classification of red cell hemolytic disorders by predominant morphology and specific red cell morphologic abnormalities

- *Acanthocytes (spur cells)*: Because of changes in membrane lipid content, these red cells have several irregularly distributed, sharp projections of unequal length. Most of the affected erythrocytes are also small and lack central pallor:
 - Spur-cell anemia
 - Liver disease
 - Uremia
 - Abetalipoproteinemia
 - Hypothyroidism
 - Heat stroke
 - DIC
 - After splenectomy or hyposplenic state
 - Vitamin E deficiency
- *Echinocytes (burr cells)*: Burr cells usually have 10–30 blunt and fairly symmetrical projections:
 - Renal failure
 - Dehydration
 - Storage artifact
 - Liver disease
- *Elliptocytes*: Elliptical cells, normochromic:
 - Hereditary elliptocytosis
 - Thalassemias
 - Megaloblastic anemias
 - IDA
- *Spherocytes*: Inherited or acquired defect in the erythrocyte membrane decreases the surface area to volume ratio:
 - Hereditary spherocytosis
 - Transfused erythrocytes
 - Autoimmune hemolytic anemia
 - Severe burns, other red cell thermal injury
 - *Clostridium welchii* septicemia
 - *Enzyme deficiency*: G6PD, pyruvate kinase deficiency
 - Hemolytic transfusion reactions
 - ABO incompatibility in neonates
 - Microangiopathic hemolytic anemia
 - Hypersplenism
- *Target cells*: Erythrocyte's center contains a circle of Hb pigment surrounded by a ring of pallor:
 - Iron deficiency
 - Hemoglobinopathies, like S, C, D and E
 - Thalassemias
 - Liver disease, like hepatitis, obstructive jaundice
 - After splenectomy

Contd...

Contd...

- *Stomatocytes*: Have a slit-like area of central pallor:
 - Hereditary stomatocytosis
 - Rh_{null} blood group
 - Malignancies
 - Liver disease, especially acute alcoholism
- *Schistocytes*: Helmet, triangular shapes, or small fragments:
 - Microangiopathic hemolytic anemia
 - DIC
 - Chemotherapy (mitomycin C)
 - Malignant hypertension
 - Hemolytic uremic syndrome
 - G6PD deficiency
 - Burns
 - Liver disease
 - Uremia
- *Heinz bodies*: Aggregated denatured Hb:
 - Thalassemia
 - Heinz body hemolytic anemia
 - Asplenia
 - Chronic liver disease
- *Teardrop cells (dacryocyte)*: Shape of drop, usually microcytic:
 - Thalassemia major
 - Bone marrow malignancy
 - Myeloproliferative syndromes
 - Newborn
- *Cabot's ring bodies*: Nuclear remnant ring configuration inclusions:
 - Lead poisoning
 - Pernicious anemia
- *Basophilic stippling*: Basophilic stippling is the presence of numerous small, purplish inclusions within erythrocytes that represent aggregates of ribosomal RNA:
 - Lead poisoning
 - Thalassemia
 - Unstable Hbs
 - Pyrimidine 5'-nucleotidase deficiency
- *Howell-Jolly bodies*: Round, purple inclusions in erythrocytes that represent DNA fragments that were once part of the nucleus of immature red cells:
 - Absent or hypofunctioning spleen
 - Macrocytic or hemolytic anemia
 - Dyserythropoietic anemia

Abbreviations: IDA, iron-deficiency anemia; Hb, hemoglobin; G6PD, glucose-6-phosphate dehydrogenase; DIC, disseminated intravascular coagulation; RNA, ribonucleic acid; DNA, deoxyribonucleic acid.

MORE ON THIS TOPIC

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Chapter 38.4

Congenital Bone Marrow Failure

Maitryee Bhattacharya, Meet Kumar

Inherited bone marrow failure syndromes (IBMFS) are a heterogeneous group of disorders characterized by bone marrow failure (BMF) along with one or more structural abnormality. Of all the aplastic anemia patients diagnosed in children and adolescents, approximately 25% of pediatric and 10% of adolescents have an inherited etiology. Identification of such patients is of utmost importance, as inherited and acquired disorders differ significantly in treatment options, outcomes and prognosis. IBMFS can be classified into those with unilineage cytopenia or those with bilineage or multilineage cytopenia.

FANCONI ANEMIA

Fanconi anemia (FA) was first described by Dr Guido Fanconi in 1927 when he noted macrocytic anemia in a family of three brothers along with varying skeletal abnormalities. FA constitutes the most common type of IBMFS (constituting almost 50%). However, reported frequency of FA of all aplastic anemia in children varies from 10% to 25% in different Indian studies.

Etiopathogenesis

Fanconi anemia is identified as a multigenic disorder. Currently 13 genes are identified and dissected.

These FA proteins function in coordination in the repair of DNA crosslinks (**Fig. 1**). There are three discrete steps in the FA DNA damage response pathway core complex. Eight wild-type FANC proteins (FANCA-C, FANCE-G, FANCL and FANCM) and few other proteins form a single large nuclear protein *core complex*, that functions as an ubiquitin ligase of which FANCL is the catalytic subunit ID complex. The activated core complex results in conversion of two downstream protein targets, FANCI and FANCD2 (called the *ID complex*), from unubiquitinated isoforms to monoubiquitinated isoforms downstream effector complexes. In normal cells after monoubiquitination of the

ID complex, the wild-type core complex translocates the monoubiquitinated ID complex to chromatin and localizes the ID complex to nuclear foci to complete the final step of the DNA repair response. Additional factors also operate in FA BMF, including telomere shortening.

Clinical Features

It is reported in larger series that 39% of FA patients have aplastic anemia and anomalies (**Figs 2A to D**), 30% have aplastic anemia without anomalies, 24% have anomalies without aplastic anemia, and 7% have neither. Frequency of common structural anomalies is shown in **Table 1**.

Table 1 Common structural anomalies in Fanconi anemia

Anomalies	Associated frequency (%)
Skin pigment changes or café-au-lait spots	40–65
Short stature	40–65
Skeletal (thumbs, hands, head, face, trunk)	40–70
Hypogonadal and genitalia changes (mostly male)	20–30
Eye, eyelid, or epicanthal fold anomalies	20–40
Renal malformations	20–35
Gastrointestinal or cardiopulmonary malformations	10–15
Ear anomalies (external and internal), deafness	~10
CNS imaging anomalies	3–10

Approach to Diagnosis

A child should be tested for FA if presents with aplastic anemia, any of the structural anomalies listed above, primary myelodysplastic syndrome (MDS) or acute myelogenous leukemia (AML) (at a young age), cancer typical of FA at an atypical age. On initial suspicion for FA, a stress cytogenetic test is usually done for diagnosis. However, if stress test is negative, but suspicion is still high, second level tests may be done for definitive diagnosis (fibroblast culture for mosaicism, complementation analysis, western blot for FANCD2 determination, flow cytometry for studying cell cycle kinetics, etc.). However, if those tests come negative, an alternative diagnosis should be considered.

Investigations

Peripheral blood and bone marrow The RBCs are macrocytic with mean corpuscular volume (MCV) often above 100 fL even before the onset of anemia. In the early stages, there is usually erythroid hyperplasia in the bone marrow (BM), with varying dyserythropoiesis and dysmyelopoiesis. As the disease progresses, the marrow becomes progressively more hypocellular.

Stress cytogenetics This test evaluates the oversensitivity of T lymphocytes of FA patients to various cell mitogens and cross-linking agents like mitomycin-C (MMC) or diepoxybutane (DEB). The stressed chromosomes show evidence of chromosomal breakage or aberrations (in the form of breaks, gaps, rearrangements, radials, triradials, quadriradials) (**Fig. 3**). There are rare disorders, such as Nijmegen breakage syndrome, in which chromosome breakage may be positive but the patient does not have FA. The blood result may also be normal in cases of mosaicism, when the test may need to be done from fibroblast.

Complementation analysis Definitive proof of FA is accomplished by identification of the gene complementation group, followed by demonstration of the disease-causing mutation.

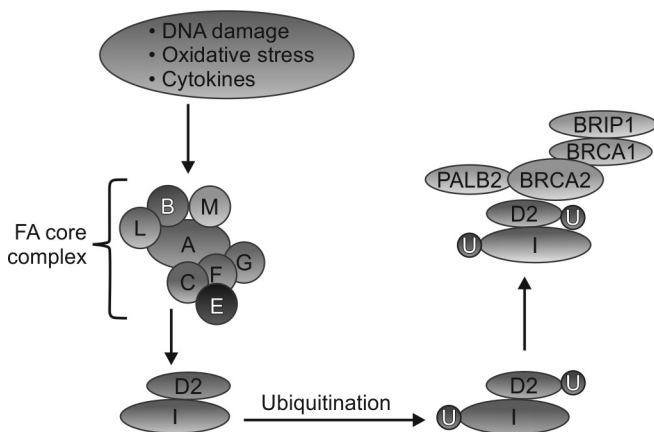


Figure 1 Fanconi anemia/BRCA DNA damage response pathway. Following DNA damage, the proteins represented by A, B, C, E, F, G, L, and M form the core complex, which is required for ubiquitination of the I and D2 proteins, which are in turn required for the downstream complex to form foci for DNA repair



Figures 2A to D Facial similarities between unrelated patients with a triangular face and micrognathia (A to C) and triphalangeal thumb abnormality (D)

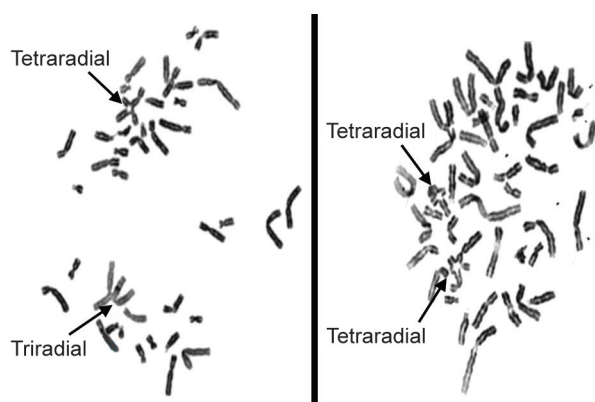


Figure 3 Patterns of chromosomes in blood treated with DNA cross-linking agents. Left, Mitomycin C, arrows show radial figures. Right, Diepoxybutane, arrows show breaks, gaps, and rearrangement figures. Source: Dr Mayur Parihar, Consultant, Department of Cytogenetics, Tata Medical Center, Kolkata.

Management and Outcome

Management of patients with FA begins with a thorough history and physical examination, laboratory tests and cancer screening. A surveillance program for solid cancers should be initiated at least annually. Dentists, oral surgeons, or head and neck surgeons should be consulted starting 10 years of age to screen for head and neck squamous cell carcinomas. At 13 years of age, all women with Fanconi phenotype should have annual gynecologic screening. Growth should be serially documented, and when growth velocity or stature is less than expected, endocrine evaluation should be done and growth hormone deficiency addressed. Recommended hematologic monitoring is to monitor blood counts every 3–4 months, with annual BM aspirates and biopsies including cytogenetics.

Treatment of BMF should be initiated as the hemoglobin falls less than 8 g/dL, platelets fall less than 30,000/ μ L, and absolute neutrophil count is less than 500/ μ L (or there are symptoms from anemia, bleeding, or infection).

Androgens

Androgen therapy has been used to treat FA for decades. The overall response rate is about 50%. Reticulocytosis occurs initially, followed by a rise in hemoglobin within 1–2 months. When an adequate response has been attained, the androgens should be slowly tapered but not stopped. Oxymetholone, an oral 17- α -alkylated androgen,

is used most frequently at 1–5 mg/kg once a day. Some prefer to add corticosteroids to control androgen-induced growth acceleration and to prevent thrombocytopenic bleeding by promoting vascular stability. Almost all patients relapse when androgens are stopped. A few noteworthy complications associated with androgen therapy include peliosis hepatis, cholestatic jaundice or elevated liver enzymes, hepatocellular adenomas, hepatocellular carcinoma (characteristically does not produce α -fetoprotein in serum) and prostatic carcinoma. Those receiving androgens should be monitored for liver enzymes periodically.

Hematopoietic Stem Cell Transplantation

Hematopoietic stem cell transplantation is the only curative therapy for the hematologic abnormalities of FA: aplastic anemia, AML, and MDS. The best donor source is an human leukocyte antigen (HLA)-matched sibling. Special precaution need be taken so as to exclude the possibility of FA phenotype in the sibling. Owing to high-risk of severe cytotoxicity from chemotherapy and irradiation and exaggerated graft versus host disease (GVHD) in these patients with the use of conventional conditioning regimens, reduced-intensity hematopoietic stem cell transplantation (HSCT) protocols have been introduced and improved outcomes achieved. Absolute indications for a matched sibling donor HSCT include severe under productive cytopenias and transfusion dependency, high-risk MDS with chromosomal clonal abnormalities or an overt AML.

DYSKERATOSIS CONGENITA

Originally it was considered a dermatologic disease and was termed Zinsser-Cole-Engman syndrome, manifesting as a diagnostic ectodermal triad of reticulate skin pigmentation of upper body, mucosal leukoplakia, and nail dystrophy. Hematologic manifestations constitute an important part and cause substantial morbidity and mortality. Dyskeratosis congenita (DKC) patients also have a predisposition to develop cancer and MDS. DKC constitutes approximately 5% of all inherited marrow failures.

Pathophysiology

Dyskeratosis congenita shows many modes of inheritance including X-linked recessive, autosomal dominant and autosomal recessive. Six DKC genes (*DKC1*, *TERC*, *TERT*, *NOP10*, *NHP2*, *TINF2*) have been identified till date. These gene products are involved in a highly conserved process of telomere maintenance pathway by which the ends of chromosomes are prevented from shortening substantially with each cell replication (**Fig. 4**). DKC with mutations in the *DKC1* (X-linked recessive DKC) or *TINF2*

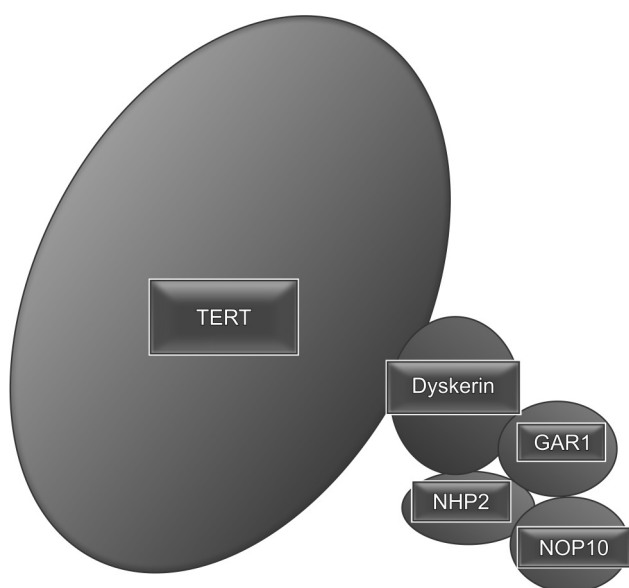


Figure 4 Telomere biology pathway with mutations in patients with Dyskeratosis congenita. Mutations in any of the proteins in telomerase complex can cause Dyskeratosis congenita. These proteins are associated with maintenance of telomere length with help of shelterin-dyskerin pathway

and biallelic *TERT* mutations (autosomal recessive DKC) can result in a severe form of DKC called *Hoyeraal-Hreidarsson syndrome*, characterized by hematologic and dermatologic manifestations of DKC in addition to cerebellar hypoplasia. *Revesz syndrome* is a combination of classical manifestations of DKC and exudative retinopathy. It is caused by mutations in *TINF2* and is an autosomal dominant form of the disease. Most studies of the pathogenesis of the aplastic anemia in DKC have shown a marked reduction or absence of colony growth factors CFU-GEMM, CFU-E, etc.

Clinical Features

Clinical manifestations often appear during childhood. Lacy reticulated skin pigmentation affecting the face and trunk is a common finding (89%) and usually appear first. Nail dystrophy of the hands and feet is the second most common finding (88%), that usually starts with longitudinal ridging and may eventually cause

nail loss. Leukoplakia is found in ~75% that usually involves oral cavity (**Figs 5A and B**). Epiphora (excessive tearing) secondary to nasolacrimal duct obstruction is common and occurs in approximately 50%.

Abnormalities of the teeth, particularly an increased rate of dental decay and early loss of teeth, are common. Skeletal abnormalities such as osteoporosis with recurrent long bone fractures and vascular necrosis are seen in approximately 20% of cases. Genitourinary abnormalities and gastrointestinal abnormalities have been reported. BMF develops in about 80% of patients by the age of 20 years. These patients are particularly prone to develop cancers usually in the 3rd and 4th decades of life. They have increased risks for MDS, AML and solid tumors with a cumulative incidence of approximately 10–30%.

Laboratory Findings

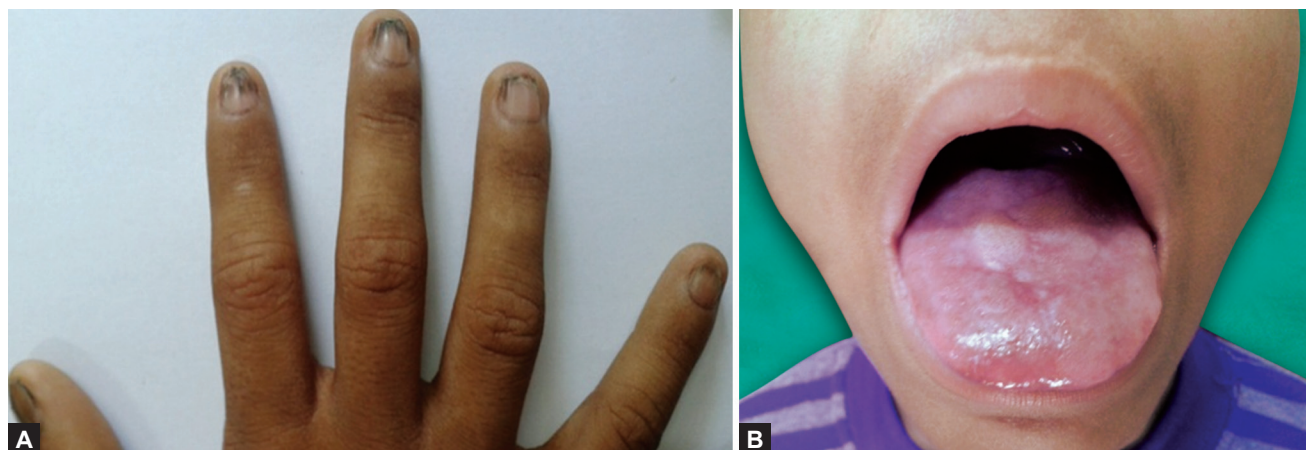
Peripheral blood and bone marrow The incidence of cytopenias caused by BMF has been reported in up to 90% of the patients. The RBCs are often macrocytic, and the fetal hemoglobin can be elevated.

Telomere length is a useful screening testing for DKC with majority showing very short telomeres, examined in leukocyte subsets using flow cytometry with fluorescence in situ hybridization. The presence of short telomeres in peripheral blood lymphocytes is suggestive for DC to be the cause of BMF but is not specific. Although patients with acquired aplastic anemia may have short telomeres in granulocytes, patients with DC have short telomeres in all leukocyte subsets and this is an important distinguishing feature.

Management

Androgens Androgens improve BM function in about 50% of patients. If a response is achieved, the androgen dose may be slowly tapered but should not be stopped. As in FA, patients typically become refractory to androgens as aplastic anemia progresses. A small number of patients may respond to G-CSF therapy.

Hematopoietic stem cell transplantation DKC is a disorder with chromosomal instability caused by defective telomere maintenance. This explains the hypersensitivity to irradiation and chemotherapy and transplantation. Further, because of the high degree of mucocutaneous involvement, DKC patients may be expected to be more susceptible to endothelial damage, which occurs after HSCT as a result of various factors. Limited data is available with HSCT due to rarity of disease.



Figures 5A and B Dyskeratosis congenita. (A) Dystrophic nails; (B) Oral leukoplakia

SHWACHMAN-DIAMOND SYNDROME

Shwachman-Diamond syndrome (SDS) is an autosomal recessive disorder characterized by exocrine pancreatic insufficiency, BMF and other somatic abnormalities (particularly metaphyseal dysostosis). It constitutes around 2% of all IBMFS.

Pathophysiology

The mutant gene responsible for this complex pleiotropic phenotype, termed Shwachman-Bodian-Diamond syndrome (SBDS), has been identified and has been confirmed in 90% of patients with the classic presentation. SBDS seems to be multifunctional and promotes cell survival, ribosome biogenesis, mitotic spindle stability, and chemotaxis. No unifying pathogenesis has been able to account for all of the multisystem features of SDS.

Clinical Features

The most common hematologic abnormality affecting 88–100% of patients with SDS is neutropenia. Roughly 10–65% of patients have pancytopenia with some patients developing aplastic anemia. Patients with SDS have an increased risk for myelodysplasia and AML. Chromosome 7 and 20q deletion abnormalities are the most common chromosomal changes in patients with SDS. Exocrine pancreatic dysfunction is hallmarks of SDS, caused by absence of acinar cells. Clinical presentation is an infant presenting with symptoms of malabsorption, steatorrhea, failure to thrive, and low blood levels of fat soluble vitamins (vitamin A, D, E, and K). For reasons that remain unclear, exocrine pancreatic function spontaneously improves over time in roughly 50% of patients. Skeletal abnormalities are also commonly reported in patients with SDS, related to abnormal development of the growth plates. Other abnormalities as neonatal cardiac manifestations and various endocrine abnormalities have also been reported including insulin-dependent diabetes, growth hormone deficiency, hypogonadotropic hypogonadism and hypothyroidism.

Approach to Diagnosis

The diagnosis of SDS is largely based on clinical phenotype, with pancreatic exocrine and BM dysfunction being the main features. Exocrine pancreatic insufficiency may be demonstrated by elevated fecal fat excretion following a 72-hour collection in the absence of concomitant intestinal or cholestatic liver disease with imaging studies showing a small or fatty pancreas. Signs of marrow failure may include intermittent or persistent neutropenia (absolute neutrophil count $< 1,500/\mu\text{L}$) documented at least 3 times over a minimum of 3 months without an apparent cause; hypoproliferative anemia with a hemoglobin concentration below the age-related normal; unexplained macrocytosis; platelet count less than $150,000/\mu\text{L}$ without alternative etiology; or hypocellular BM. Definitive evidence is provided by sodium dodecylbenzenesulfonate (SDBS) genetic testing, however 10% of patients with clinical features of SDS may lack these mutations.

Management

General Peripheral blood counts should be monitored for cytopenias every 3–4 months. Marrow evaluation with aspirate and biopsy to assess for marrow cellularity and progression should be done yearly. For exocrine pancreatic insufficiency, most patients require oral pancreatic enzyme supplementation. However, since steatorrhea resolves in 50% of patients; assessment of continued need for pancreatic enzyme supplementation should be routinely done.

Supportive care Steroids and androgens have been shown to be effective in inducing hematologic improvement in 50%. Anemia

and thrombocytopenia should be managed with transfusions of RBCs or platelets.

Hematopoietic cell transplantation The only definitive therapy for marrow failure, MDS or leukemia is hematopoietic cell transplantation (HCT). In a large HCT registry for SDS patients for varied indications (severe aplastic anemia, MDS/AML, or other diagnosis), overall survival was 65%, with a median follow-up of 1.1 years.

CONGENITAL AMEGAKARYOCYTIC THROMBOCYTOPENIA (CAMT)

Patients with amegakaryocytic thrombocytopenia lack any characteristic birth defects. Patient usually present with platelet-type bleeding tendency from early infancy, however, serious bleeding may also be associated. Sometimes, a fraction of patients may tend to evolve to aplastic anemia, MDS or even acute myeloid leukemia without developing thrombocytopenia. It has been estimated that approximately 50% of patients develop aplastic anemia by the age of 5 years. The underlying genetic defect identified in these patients is a bi-allelic mutation in the *MPL* gene that encodes for thrombopoietin (TPO) receptor. TPO is an essential integral master regulator of megakaryocytopoiesis and platelet production. Hematopoietic stem cell transplant remains the only curative therapy for this disorder. Importantly, severe toxicity associated with conditioning regimens has not been found in patients suffering from these disorders. No increased rate of transplant-related toxicity has been reported in these patients.

UNILINEAGE CYTOPENIAS

Diamond-Blackfan Anemia

Diamond-Blackfan anemia (DBA) is a rare group of IBMFS, characterized by failure to produce red cell, presence of congenital anomalies, and cancer predisposition. DBA is now long recognized and being established as belonging to the class of disorders known as ribosomopathies. It constitutes around 15% of all IBMFS.

Pathophysiology Mutations in *RPS19*, *S24*, *S17*, *RPL5*, *L11* and *L35A* have been identified in approximately one-third of patients with DBA. These are critical for normal maturation of rRNA because its deficiency causes defective cleavage of the pre-rRNA and abnormal maturation of the 40S subunit. This leads to accumulation of faulty pre-40S ribosome subunits.

Clinical features About 30–45% of patients present with one or more congenital anomalies. Most of these phenotypic abnormalities can be divided as either craniofacial dysmorphism (hypertelorism, microcephaly, microphthalmos); prenatal or postnatal growth failure; neck anomalies (pterygium colli or Klippel-Feil syndrome or Sprengel deformity); and thumb malformations (bifid thumb, duplication, subluxation). A typical DBA facies has been described and consists of two-colored hair, snub nose, wide-set eyes, a thick upper lip, and an intelligent facial expression. Rare anomalies include urogenital malformations (dysplastic or horseshoe kidneys, duplication of ureters), congenital heart disease (ventricular and atrial septal defects), or hypogonadism, and ear malformations.

Diagnosis The diagnostic criteria for DBA, presented first in 1976 by Diamond et al., are still followed. These include presentation with anemia (before first birthday), with near normal neutrophil and/or platelet counts, reticulocytopenia, macrocytosis and normal marrow cellularity with a paucity of red cell precursors. Progression to pancytopenia is rare but may occur. Majority of patients have an increased level of red cell adenosine deaminase (ADA) enzyme levels, and signify fetal red-cell phenotype. It is a sensitive test as up to 10% patients may have normal levels. Hemoglobin F levels are often elevated, although this is a nonspecific finding.

Management Current mainstays of treatment are red cell transfusions, corticosteroid therapy, and HSCT. A majority of DBA patients will respond to steroid therapy, although a few 20% of patients might not respond and will require prolonged red cell transfusions for recurrent anemia. Such patients need to be monitored for side effects of chronic transfusion like infection transmission, alloimmunization and iron overload. Iron chelation therapy need to be resorted to if serum ferritin levels increase beyond 1,000 ng/mL. One fourth of patients have been reported to undergo what is known as *spontaneous remission*, and may not require any therapy. It may be advisable to transfuse during initial growth years to maintain adequate growth spurt, but the side effects of transfusion therapy need to be balanced against the benefits.

Corticosteroid may be started at 2 mg/kg/day, for a maximum trial of 4 weeks. An adequate response is considered as a hemoglobin level greater than 9 g/dL independent of transfusion. In case of response, steroid taper should ensue. Definitive therapy for DBA, like other IBMFS, is stem cell transplantation. Allogeneic matched sibling HSCT has been very successful. The data from the Diamond-Blackfan Anemia Registry of North America (DBAR) reveal an overall survival of 77% for sibling HSCT and 31% for alternative donor HSCT. After HSCT, periodic phlebotomy should be done, when the hemoglobin permits, to eliminate residual iron burden.

Congenital Dyserythropoietic Anemia

The designation congenital dyserythropoietic anemia (CDA) refers to a family of inherited refractory anemia characterized by BM erythroid multinuclearity, ineffective erythropoiesis, and secondary hemosiderosis. The ineffective erythropoiesis is reflected by BM erythroid hyperplasia, inappropriately low reticulocyte counts for the degree of anemia, and intramedullary RBC destruction. Splenomegaly and chronic or intermittent jaundice are additional features. Granulopoiesis and thrombopoiesis are normal. Three classical forms of CDA have been described (**Table 2**).

There are additional, less common groups (and not types) of CDA that are identified when classification into the above groups is not possible (CDA groups IV to VII). These are classified on the basis of morphology rather than genotypic features, and can vary in presentation from severe macrocytosis with no anemia (as in CDA group VI) to severe transfusion dependent anemia since birth with normocytic normochromic indices (as in CDA group VII).

Kostmann Syndrome

Patients with severe congenital neutropenia (SCN) typically present with recurrent life-threatening infections in the first few months of life. Diagnosis is established by persistent low neutrophil counts of less than 500/ μ L for at least 3 months after exclusion of acquired causes of neutropenia. Most common genetic mutation identified in these patients is the heterozygous ELANE mutations found in 30% of patients. BM examination shows a maturation arrest in the neutrophilic and myeloid lineage. Rarely, the disease can progress to myelodysplasia and leukemia. It constitutes roughly 17% of

all IBMFS. Other gene mutations have been identified including mutations in *G-CSF*, *GFI1*, *WASP* and *HAX1*. The importance of identifying ELANE mutations lies in the tendency to progress to acute leukemia at a much higher rate than in other mutations. The treatment of neutropenia in patients with SCN is G-CSF, to which most respond with improved neutrophil counts. The aim is to raise the count to above 1,500/ μ L.

Thrombocytopenia Absent Radii

As the name suggests, patients present with bleeding manifestation due to thrombocytopenia and typically bilaterally absent radii (although in less than 5% cases, radii may be absent unilaterally). An important distinguishing feature from FA is that in thrombocytopenia absent radii (TAR) thumbs are usually present, while they will be absent in FA if the radii are absent. The genetics of TAR is not clear. A few studies have identified interstitial deletion of 200 kb on chromosome 1q21.1, although the incriminating gene is not the only gene involved and search for other affected genes is still an active research area. Patients may have other birth defects like hypoplastic ulnae, hypoplastic humeri, phocomelia, bowed legs, hip dysplasias, abnormal facies, renal malformations, etc. Marrow examination usually reveals absent or small and abnormal megakaryocytes; other lineages being normal. Few patients may require platelet transfusions, and a very occasional patient may also require red cell transfusion support, however, the usual clinical course is a trend of increase in platelet counts by 1 year of age. Stem cell transplantation is a very rare requirement.

IN A NUTSHELL

1. Marrow failure syndromes are a rare group of diseases that need high index of suspicion for early diagnosis and intervention.
2. Most of these syndromes are associated with some genetic predisposition.
3. History should include evaluation regarding symptoms of malabsorption, GI symptoms, pulmonary symptoms, frequent infections, developmental delays, drug intake and exposure to other marrow toxins.
4. A clinical exam should focus on facial features, skeletal abnormalities such as thumb and radius, hair loss, skin pigmentation changes, leukoplakia, nail dystrophy and structural cardiac, pulmonary and genitourinary abnormalities.
5. A laboratory examination should aim confirmation of diagnosis with blood counts and peripheral smear examination, reticulocyte count, bone marrow aspiration and biopsy, cytogenetics including stress cytogenetics, flow cytometry for CD55/CD59, routine biochemistries and HLA-typing.
6. Although steroids and androgens show efficacy in few patients, definitive therapy for most patients remains bone marrow transplantation.

Table 2 Congenital dyserythropoietic anemia types

	Type I	Type II	Type III
Inheritance	AR	AR	AD, AR
RBCs	Macrocytic	Normocytic	Macrocytic
Erythroblast LM	Megaloblastic, internuclear bridges	Normoblastic, binuclearity	Megaloblastic, up to 12 nuclei per cell
Ham test	Negative	Usually positive	Negative
Gene location	15q15	20q11	15q21

MORE ON THIS TOPIC

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Chapter 38.5

Aplastic Anemia

Amita Mahajan

Aplastic anemia (AA) refers to bone marrow (BM) failure leading to pancytopenia. It is characterized by a hypocellular marrow without fibrosis or dysplasia. This includes congenital BM failure syndromes, which together to represent about 10–30% of all patients with AA. The vast majority of children with AA, however, have acquired AA which is being covered in this chapter. We have already discussed the congenital BM failure syndrome in the previous chapter. With current management strategies, the outcome in acquired AA has improved dramatically.

EPIDEMIOLOGY

The incidence of acquired AA from North America and Europe is 2 in 1 million children per year. The reported incidence in Asia is at least two to three times higher and incidence as high as 14 per million has been reported from Japan. Data available from India is largely hospital based rather than being population based but is again consistent with the incidence being much higher than that reported from the developed world.

ETIOLOGY

A number of drugs, toxins, infectious agents, radiation and immune disorders are linked to AA. **Box 1** lists the common offending agents. The most common identifiable preceding event in India is seronegative hepatitis. However, most patients do not have a well-defined precipitating factor and are referred to as idiopathic AA. A careful history for known offending agents should always be taken. Even in the absence of classical physical findings, inherited BM failure syndromes should always be considered and excluded by appropriate tests before initiating the treatment.

BOX 1 Etiology associated with acquired aplastic anemia

- Hepatitis B, C, seronegative hepatitis
- Human immunodeficiency virus (HIV)
- Cytomegalovirus
- Epstein-Barr virus (EBV)
- Parvovirus
- Mycobacterial infections
- Human herpesvirus 6 (HHV-6)
- Varicella zoster virus
- Measles, adenovirus
- *Drugs:*
 - Chemotherapy drugs
 - Chloramphenicol, nonsteroidal anti-inflammatory drugs (NSAIDs), antibiotics, anticonvulsants, sulfonamides, gold salts
- *Chemicals:*
 - Benzene, insecticides, pesticides, solvents
- Radiation
- Autoimmune disorders, e.g., systemic lupus erythematosus (SLE)
- Paroxysmal nocturnal hemoglobinuria (PNH)

PATHOPHYSIOLOGY

It is now well established that the pathogenesis of acquired AA is immune mediated. The pathophysiology responsible for marrow destruction has been inferred from the results of immunosuppressive therapy (IST). Hematological improvement after IST implicated the immune system in the destruction of progenitor stem cells. Results from numerous studies have

demonstrated increased cytokine expression, low CD4 regulatory T-cells, oligoclonal CD8 cytotoxic T-cells, and expansion of specific CD4 cell populations in the BM of AA patients. The antigens inciting the aberrant immune response have not been identified. However, recently a likely genetic signature of immune escape has been identified in the form of acquired number-neutral loss of heterozygosity of the short arm of chromosome 6 (6pLOH). These findings have strengthened the belief that BM aplasia in acquired AA is immune mediated. Indeed, the terminology should be *immune-mediated AA* but as convention it is being termed as idiopathic AA.

CLINICAL FEATURES

Most children present with signs and symptoms related to pancytopenia. Thrombocytopenia may manifest as easy bruising or petechiae or occasionally as epistaxis or menorrhagia. Pallor, lethargy, and weakness secondary to anemia are the other common presenting features. Overt infection at presentation is infrequent even in the presence of severe neutropenia. There may be history of single lineage cytopenia, for a length of time prior to development of pancytopenia. Mean corpuscular volume is normal or increased. The reticulocyte count is markedly reduced. In addition, routine workup for a child with pancytopenia should include liver and kidney function tests. Also, megaloblastic anemia should be ruled out as this continues to be the most common cause of pancytopenia in India because of the dietary habits of large sections of the Indian population.

DIAGNOSIS AND SEVERITY

Diagnosis is established on BM biopsy which reveals a markedly hypocellular BM with increased fat spaces (**Fig. 1**). Ideally paroxysmal nocturnal hemoglobinuria (PNH) should be ruled out by doing the Ham test or preferably by flow cytometric studies. In selected cases, workup for autoimmune diseases may be indicated if clinical features suggest an underlying autoimmune disorder. Appropriate test should be undertaken to determine the etiology as and when indicated. The severity of AA is graded on the basis of BM cellularity, absolute neutrophil count (ANC) and platelet count. Patients with ANC less than 500/ μ L, platelet count less than 20,000/ μ L, corrected reticulocyte count less than 1% and BM cellularity less than 25% are classified as having severe AA. Patients with these features but an even lower ANC of less than 200/ μ L are classified as very severe AA. **Table 1** shows the classification based on severity.

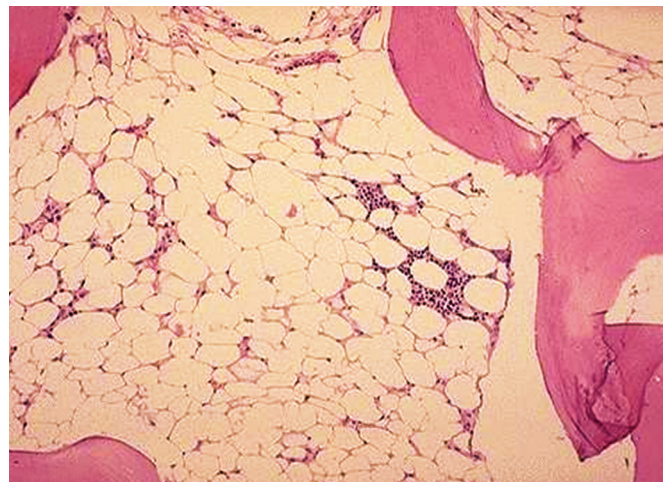


Figure 1 Markedly hypocellular bone marrow in aplastic anemia

Table 1 Definition of severity of aplastic anemia (AA)

Moderate or nonsevere AA (NSAA)	Decreased BM cellularity and peripheral blood cytopenia not fulfilling the criteria for SAA
Severe AA (SAA)	BM cellularity < 25% and at least two of the following: <ul style="list-style-type: none"> • Absolute neutrophil count (ANC) < 500/μL • Platelet count < 20,000/μL • Corrected reticulocyte count < 1%
Very severe AA (vSAA)	Fulfilling criteria for SAA but ANC < 200/ μ L

DIFFERENTIAL DIAGNOSIS

Acquired AA should be differentiated from inherited BM failure syndromes. All children with AA should have a chromosomal breakage analysis at least a few weeks after a transfusion to avoid a falsely negative result. Acquired AA also needs to be differentiated from hypoplastic myelodysplastic syndrome (MDS). Telomere length analysis is the test of choice to rule out dyskeratosis congenita but is not widely available. Megaloblastic anemia should always be considered in children with pancytopenia but in these patients, the BM is, in fact, hypercellular. Transient BM suppression following viral illness may also manifest as pancytopenia but this is usually self-limited and recovers spontaneously.

MANAGEMENT

Mild to Moderate Aplastic Anemia

The vast majority of children with acquired AA actually have severe AA. A proportion may, however, have mild to moderate AA. Though the clinical course of these patients is variable, most of these will eventually progress to develop severe AA. A small proportion may achieve remission and therefore management should be judicious. Mild to moderate AA is usually seen in inheritable marrow failure syndromes and these must be ruled out in this clinical situation. In the short term, some of them may respond to milder therapies in the form of androgenic steroids if there is residual hematopoietic function, cyclosporine alone, or thrombopoietic agents. At least in some patients, moderate AA results from telomere gene mutations and stem cell exhaustion and androgens have been shown to increase telomerase activity through estradiol receptors and this may explain their mechanism of action in stimulating marrow function.

In the past, colony stimulating factors were tried in this situation. This however carries the serious risk of developing myelodysplasia and therefore they are no longer routinely recommended but used sparingly to overcome acute infective episodes. Daclizumab, a humanized monoclonal antibody to the interleukin-2 receptor, has shown some success in this setting with relatively little toxicity.

The use of immunosuppression with agents such as cyclosporine is not entirely without side effects. Patients may experience hirsutism, nephrotoxicity, or hypertension. If the patient is asymptomatic, it may be prudent to keep them under close observation. The definitive treatment is however, identical to that of severe AA.

Severe Acquired Aplastic Anemia

The primary treatment options for children with AA are allogeneic hematopoietic stem cell transplantation (HSCT) or immunosuppressive therapy (IST). Allogeneic HSCT with a matched family donor if feasible is currently the treatment of choice for these patients. If done early in the course of disease before the onset of infectious complications, the survival is as high as 90%. The preferred conditioning regimen is cyclophosphamide

and antithymocyte globulin (ATG). This conditioning regimen results in decreased graft versus host disease and improved long-term survival in comparison with regimens that include total body irradiation. Another conditioning regimen being increasingly used is fludarabine and cyclophosphamide with good results.

Patients, for whom, a matched family donor is not available, IST with horse-ATG (hATG) with cyclosporine is the preferred treatment. A short course of steroids is given to prevent serum sickness. There is now ample data that the response rate is superior if hATG is used in comparison to rabbit-ATG (rATG). Cyclosporine is given for 12 months and then tapered slowly over a few months. The response rate in children is better than that seen in adults and reported to be in excess of 60%. Some recent studies have reported response rates of 70–80%. This includes complete response, i.e., normalization of blood counts and partial response wherein patients may continue to have relatively low counts but are transfusion independent. **Table 2** enumerates definitions of response to IST. The major concerns with regards to IST are the risk of clonal evolution and development of myelodysplasia and leukemia. Algorithm for treatment of AA is given in **Flow chart 1**.

With improved results from matched unrelated donor (MUD) transplants and increased availability of unrelated donors from various registries, this is another option that can be actively considered in these patients and may eventually become frontline therapy. Recently, favorable results have been reported from haploidentical transplants in patients who have failed to IST. This is an exciting development, especially for countries where BM donor registries are not fully developed, as potentially this could mean that every patient has a potential donor.

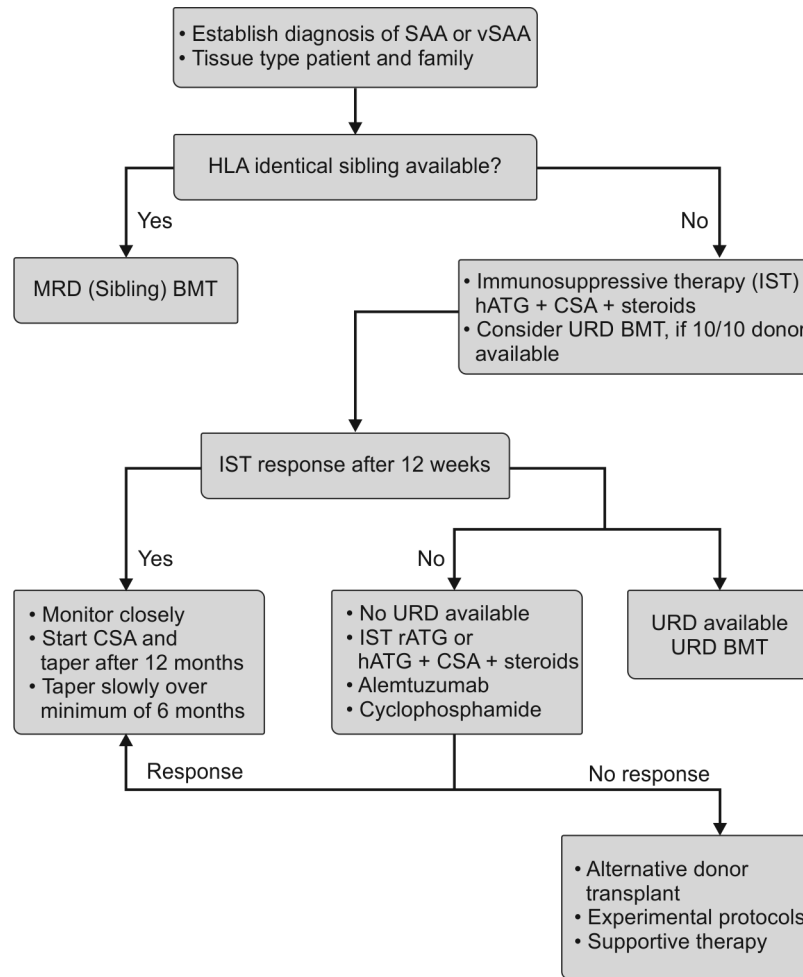
For those, wherein unrelated transplant is not feasible, a second course of IST with hATG or rATG may achieve a response in a proportion of patients. A second course may also be warranted in those who relapse after a length of time. Both allogeneic bone marrow transplant (BMT) and IST are highly myelosuppressive and immunosuppressive and need to be carried out in specialized centers. Allogeneic BMT carries with it the risk of graft rejection, severe infections and graft versus host disease which may be potentially fatal. IST, with cyclosporine, usually needs to be continued for 6–12 months. IST with cyclosporine can be associated with severe infusional reactions, anaphylaxis, severe infections and serum sickness in the short term. Patients undergoing both these treatments are also susceptible to severe viral infections, e.g., cytomegalovirus (CMV), and are also at risk of Epstein-Barr virus-associated lymphoproliferative disease.

Other immunosuppressive agents such as mycophenolate mofetil, sirolimus and alemtuzumab have been tried but have not demonstrated superior responses or reduced incidence of clonal evolution. Cyclosporine alone has been tried and may show a response rate in a small proportion of patients. High-dose cyclophosphamide without stem cell support has been used by some centers with good response rates. However, this is associated with prolonged neutropenia and morbidity and is usually considered only as second- or third-line therapy.

Table 2 Definitions of response after immunosuppressive therapy (IST)

Complete response (CR)	ANC > 1,500, platelet > 100,000, Hb > 11 g/dL
Partial response (PR) in SAA	ANC > 500, platelet > 20,000, Hb > 8 g/dL
PR in moderate AA	ANC > 1,000, platelet > 30,000, Hb > 8 g/dL
Overall response	CR or PR 6 months after IST

Abbreviations: ANC, absolute neutrophil count; SAA, severe aplastic anemia; AA, aplastic anemia.

Flow chart 1 Treatment algorithm for acquired aplastic anemia

Abbreviations: SAA, severe aplastic anemia; vSAA, very severe aplastic anemia; HLA, human leukocyte antigen; MRD, matched-related donor; hATG, human antithymocyte globulin; CSA, cyclosporine; URD BMT, unrelated donor bone marrow transplantation; rATG, recombinant antithymocyte globulin.

Recently, eltrombopag, a thrombopoietic agent has been shown to improve hematopoiesis in a proportion of patients with adult AA who were refractory to IST and is currently being evaluated in this setting.

Supportive Care

The significant improvement in the overall survival of children with AA is at least partly attributable to marked improvements in supportive care. Infections and bleeding are the major cause of morbidity and mortality in this cohort.

Transfusions

The transfusion policy in AA is generally restrictive. Most centers transfuse packed red cells if hemoglobin is less than 10 g/dL or if child is symptomatic. Leukodepleted and irradiated blood products should be given to reduce the risk of transfusion-associated graft-versus-host disease and human leukocyte antigen (HLA) sensitization. Also, immediate family members should be avoided as donors if an allogeneic stem cell transplant from a matched family donor is being contemplated. Platelet transfusions are considered, if platelets are less than 10,000/ μ L or there is symptomatic bleed. Higher thresholds (i.e., < 20,000/ μ L) may be considered for those being managed for sepsis or undergoing IST.

In life-threatening situations, granulocyte transfusions may be considered to provide a bridge between treatment response and neutrophil recovery.

Prophylaxis from Infections

There is no evidence to support the role of antibiotics for prophylaxis in this patient population. However, a number of precautions are routinely prescribed for these patients. **Table 3** lists the precautions that are commonly recommended for these patients. Prompt administration of intravenous antibiotics in the event of fever or other signs of infection is the cornerstone of management of neutropenic fever in this population. The choice of first-line antibiotics is usually a third-generation cephalosporin with or without an aminoglycoside. The choice of first-line antibiotic depends on the known sensitivity pattern in a given hospital. Subsequent management is as for other patients with neutropenic fever as per pre-established hospital guidelines.

Prophylactic antifungals are however routinely used for patients with prolonged neutropenia on immunosuppressive treatment. Posaconazole is considered to be the drug of choice for antifungal prophylaxis. For patients with suspected fungal infection or persistent fever, computed tomography of chest and galactomannan testing are recommended and empiric treatment

Table 3 Principles of neutropenic precautions for pediatric aplastic anemia (AA) patients

Avoid	Construction areas, compost, potted plants, unpasteurized dairy products, uncooked meat products, unwashed raw fruits or vegetables, crowded areas, live vaccines
Recommended	Frequent hand washing, guidelines for body hygiene, prophylactic antifungals, G-CSF when on IST
In hospital	Air quality control, barrier isolation

Abbreviations: G-CSF, granulocyte-colony stimulating factor; IST, immunosuppressive therapy.

is started. Antifungal treatment is largely directed at *Aspergillus* and possible strategies include use of voriconazole/amphotericin B/caspofungin.

Pneumocystis prophylaxis is to be considered for those with severe lymphopenia [absolute lymphocyte count (ALC) < 500/ μ L] especially following IST. The drug of choice for pneumocystis prophylaxis is cotrimoxazole but is difficult to use in view of myelosuppressive effect. The options are pentamidine nebulization or dapsone.

Granulocyte-colony stimulating factor (G-CSF) is not routinely recommended in AA. However, it may be considered in patients with active infection and is routinely used by some centers following IST. Prolonged use may increase the chances of clonal hematopoiesis and malignant transformation to MDS/acute myeloid leukemia and is discouraged.

LONG-TERM OUTCOME

As the numbers of children with AA that are successfully being treated with BMT or IST are increasing, there are concerns regarding long-term outcome and late effects of successful therapy. For patients undergoing BMT, these include growth failure, infertility, and chronic graft-versus-host disease. For those undergoing IST, the biggest concern is the development of PNH, MDS and leukemia which can develop after many months to years. The cumulative long-term rate of clonal evolution is about 15% and this risk is highest in those who receive chronic G-CSF therapy.

One of the key concerns following treatment of AA with BMT is development of late malignancies. In a series from Japan, of 329 children who underwent allogeneic BMT, 5 (2.5%) developed a malignancy over a 20-year follow-up period (malignant peripheral nerve sheath tumor, thyroid carcinoma, colon carcinoma, MDS and hepatoblastoma). Essentially all children who undergo treatment for AA need to be on ongoing follow-up even if cured of AA.

PROGNOSIS

The outcome of patients with inherited BM failure syndromes is variable depending on presentation, treatment strategies employed and the eventual development of malignancy in a proportion of patients. Prognosis has, however, improved significantly with improved supportive care, improved access to transplant and active surveillance for possible malignancies.

The prognosis of acquired AA has improved dramatically with current management strategies. If a matched donor is available and an HSCT is done at appropriate time, the overall survival is in excess of 80–90%. For those who receive IST, over 60% can be

expected to be long-term survivors. In fact, a number of studies report response rates as high as 75%. The success rate for MUD and haploidentical transplants has also offered potentially curative options to these patients.

There is however the concern regarding clonal evolution of hematopoiesis and development of PNH in about 10–20% of AA patients especially in patients who receive IST and this may develop several years after treatment. There is also increased risk of development of autoimmune disease (10%) and solid tumors (11%). Thus, children with AA should be followed up indefinitely irrespective of the treatment modality used.

Long-term survival rates among children diagnosed with severe AA are excellent due to the success of HLA-identical related HSCT, concurrent advances in IST, and improved supportive care. The challenge in making treatment recommendations for children with severe AA, therefore, is to balance the apparent chronicity and morbidity following IST, with the potential up-front toxicity and complications of HSCT.

IN A NUTSHELL

1. Though a number of triggering events are known, the majority of children with acquired AA have idiopathic immune-mediated AA.
2. With current treatment strategies, the long-term outcome of aplastic anemia has improved dramatically.
3. The treatment of choice for all patients with AA is matched related HSCT.
4. For patients with acquired AA who do not have a matched related donor, IST is the treatment of choice.
5. For patients refractory to IST, MUD transplantation or haploidentical transplantation are potentially curative options.
6. Optimal supportive care remains a cornerstone of therapy prior to, during and following definitive therapy.
7. Irrespective of the treatment modality used, these patients need to be followed for life.

MORE ON THIS TOPIC

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Chapter 38.6

Iron Deficiency Anemia

Mamta Manglani

Iron is required for multiple cell functions, including DNA synthesis, oxygen transport and cellular energy production. Various iron-containing proteins are hemoglobin (Hb), myoglobin, cytochrome c, cytochrome P-450, catalase, myeloperoxidase, cyclooxygenase, and ferritin lipoygenase. Certain enzymes are iron-dependent, viz., aldehyde oxidase, nicotinamide adenine dinucleotide phosphate (NADP) dehydrogenase, tyrosine hydroxylase, succinate dehydrogenase, tryptophan hydrolase, xanthine oxidase, ribonucleotide reductase, NADPH ubiquinone oxidoreductase, NADPH succinate oxidoreductase, and *cis*-aconitase. Of the various nutrient deficiencies, iron deficiency is the most common cause of anemia worldwide.

IRON METABOLISM

Factors Affecting Iron Absorption in the Gut

Heme iron is not affected by presence of any factors in the gut. The absorption of nonheme iron is retarded by an alkaline pH, presence of phosphates, phytates, bran, starch, tannins, calcium, antacids, other metals (Co, Pb), etc. It is enhanced by ascorbic acid, free hydrochloric acid, presence of sugars and amino acids in the diet, presence of heme iron (nonvegetarian source of iron) and ethylenediaminetetraacetic acid (EDTA). Phytates, which constitute 1–2% of many cereals, nuts and legumes, play a major role in the causation of nutritional anemia in the developing world (Fig. 1).

Bioavailability of Iron in the Food

The bioavailability of iron from a particular dietary source affects the amount absorbed. Ferrous iron is better absorbed compared to ferric iron. It is estimated that in wheat-based diet, iron absorption is around 2% and in rice-based diet, it is 5–13%. Poor bioavailability of iron in largely cereal-based diet is a major cause of iron deficiency anemia (IDA) in most developing countries. Fish, meat and poultry are good sources of iron and bioavailability is around 20–30%. Increasing the dietary intake to meet the caloric needs will also increase the dietary intake of iron by one-third. Calcium in the form of milk, cheese or calcium added to the bread depresses iron absorption.

Absorption: Mucosal Cell Control Theory

The major regulation of iron cycle occurs through control of absorption since there is hardly any excretion via a physiological

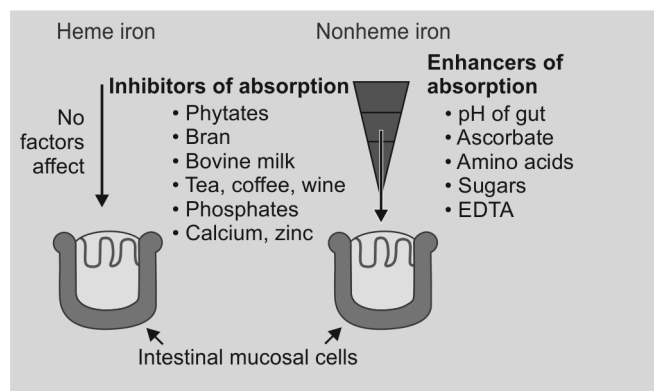


Figure 1 Factors affecting iron absorption

mechanism. Iron is available in the ferric form in diet. This is reduced to ferrous form by duodenal cytochrome b reductase (Dcytb) in the lumen of the proximal small intestine. The iron molecule that is taken into the mucosal cell across the brush border binds either with the apoferritin molecule (when iron status is adequate) or with the transferrin (when iron is required by the body). The transferrin bound iron is then released to the ferroportin at the basolateral membrane to be transported across into the circulation. Also, simultaneously, ferrous iron has to be oxidized to ferric state again during basolateral membrane transfer and this occurs through the multicopper ferroxidase hephaestin. It again binds to transferrin in circulation to be transported to various sites of synthesis of iron-containing proteins and enzymes. Iron bound to apoferritin remains in the mucosal cell and gets denuded with the cell within 3–4 days. If iron is required in the body, it is bound to the ferroportin, which is then transferred to the transferrin (produced in the liver), which carries it across the mucosa (Fig. 2). It is then utilized in the bone marrow for Hb production, in the muscle tissue for myoglobin and in the body for various other enzymes. Any excess iron is stored in the form of ferritin in the liver.

Role of Hepcidin

Since there is no excretory mechanism for iron in the body, absorption is regulated at the cellular and systemic level hepcidin, a 25 amino acid hormone synthesized in the liver, is responsible in balancing the enterocyte as well as the macrophage release of iron to maintain iron homeostasis. Hepcidin inhibits the absorption of iron at the intestinal level through internalizing ferroportin, the key molecule for transporting the iron in the ferrous form across the brush border of the intestinal villi. Thus, it blocks the binding of ferroportin to the iron molecule and prevents absorption. Also, it prevents release of iron through the same mechanism at the storage level in the macrophages. TMPRSS6 (liver-expressed type 2 transmembrane serine protease) normally inhibits hepcidin through cleaving of bone morphogenetic protein (BMP) coreceptor hemojuvelin. In vitro, TMPRSS6 expression is upregulated by hypoxia and iron deficiency. However, one of the genetic variants of TMPRSS6 leads to the downregulation of the inhibition of hepcidin. This causes an overexpression of hepcidin and therefore inhibition of iron absorption causing a refractory iron deficiency state. Role of hepcidin in iron absorption is summarized in Box 1.

Iron Cycle in Body

The RBCs circulate for their life span of approximately 120 days and are then destroyed in the spleen, liberating free iron, which is then retransported to the bone marrow and other tissues for its

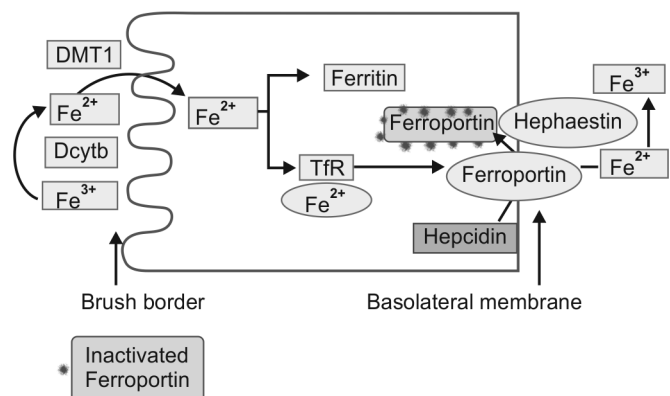


Figure 2 Mucosal cell control of iron absorption

Abbreviations: DMT, divalent metal transporter; Dcytb, duodenal cytochrome b reductase; TfR, transferrin receptor.

BOX 1 Role of hepcidin in iron metabolism

- Increased hepcidin production
 - Reduced iron absorption through internalizing ferroportin, preventing transfer of iron across the basolateral membrane and preventing mobilization of iron from stores
- Decreased hepcidin production
 - Increased dietary iron absorption
 - Increased mobilization of iron from stores

reutilization. Thus, most of the iron is cycled continuously in the body, with only 1–1.5 mg/day of iron being excreted through the intestinal epithelial cells after completion of their life span (**Fig. 3**). Since 10% of ingested iron is absorbed and the daily loss is only 1–1.5 mg, one needs to ingest about 10 mg of iron daily, except during periods of extra needs.

Foods Containing Iron

Foods rich in iron are green leafy vegetables, jaggery, cereals especially ragi, dates, almonds, nuts, sprouts, nonvegetarian sources such as pork, veal and other red meats, especially

liver. Though breastmilk contains small amount of iron, the bioavailability of this iron (lactoferrin) is about 50–70% and hence, it is adequate for the first 4–6 months of life.

EPIDEMIOLOGY OF IRON DEFICIENCY ANEMIA

It is estimated that iron deficiency affects about 30% of the world population and about 70–90% in the developing countries, including India (**Tables 1 to 4**). IDA is most common in the age group of 6 months to 3 years and 12–17 years (adolescence). It is also significantly common among pregnant and lactating women, thus compromising the iron stores in their infants. IDA can occur due to decreased absorption, increased demand or high losses from body (**Box 2**).

CLINICAL MANIFESTATIONS

Clinical features of IDA are similar to those due to anemia of any etiology. However, besides anemia, iron deficiency affects a number of other systems in the body. These include neurotransmitters (cognitive dysfunction), epithelial tissues, etc. Children with IDA generally present with symptoms depending on the rate of fall of

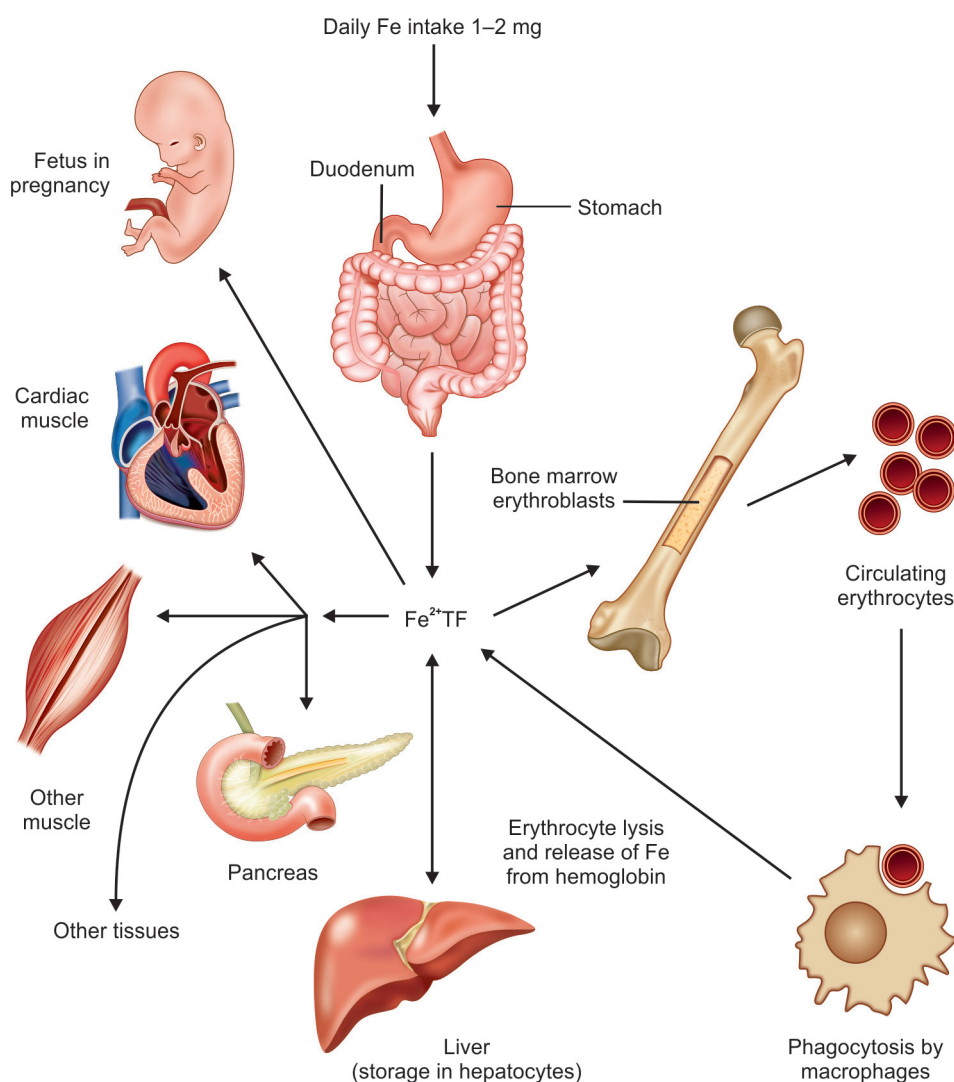


Figure 3 Iron cycle in the body (*Nature Reviews Genetics*)

Source: Reprinted with permission from: Andrews NC. Iron homeostasis: insights from genetics and animal models. *Nat Rev Genet.* 2000;1:208–17.

Table 1 Prevalence of anemia in India and neighboring countries

Country	Proportion of population with anemia (Hb < 11 g/dL)	Public health problem
Bangladesh	47.0	Severe
Bhutan	80.6	Severe
India	74.3	Severe
Nepal	78.0	Severe
Pakistan	50.9	Severe
Sri Lanka	29.9	Severe

Source: WHO Global Database on Anemia.

Table 2 Prevalence of anemia in children and women (NFHS-3 data)

Age groups	Prevalence of anemia (%)
Children (6–35 months)	79.0
Children (6–59 months)	69.5
All women (15–49 years)	55.3
Ever married women (15–49 years)	56.0
Pregnant women (15–49 years)	58.7
Lactating women (15–49 years)	63.2
Adolescent girls	
12–14 years	68.6*
15–17 years	69.7*
15–19 years	55.8

Source: National Family Health Survey (NFHS)–3;2006.

*National Nutrition Monitoring Bureau Survey (NNMBS), 2006

BOX 2 Causes of iron deficiency anemia*Reduced absorption*

- Nonbreastfed infants on cow's milk
- Inadequate intake of iron-containing foods
- Diet containing low iron or nonbioavailable iron
- *Malabsorption of iron*: Chronic diarrhea, celiac disease, cow's milk allergy, gastrointestinal (GI) surgery, giardiasis, etc.
- TMPRSS6 genetic variant leading to reduced inhibition of hepcidin and therefore overexpression of hepcidin

Increased requirement

- During periods of growth—preterm infants, toddlers, puberty
- During reproductive age in females
- Pregnancy and lactation

Increased losses

- Blood loss due to any cause
 - Gastrointestinal bleeding
 - Diverticulitis (polyps, fetomaternal hemorrhage, etc.)
 - Repeated blood sampling
 - *Menstruating women*: It is estimated that about 20% of women require ≥ 2 mg of iron per day
 - Intestinal parasites—hookworm infestation

Inadequate transport

- Atransferrinemia
- Antitransferrin receptor antibodies

Hb and homeostatic adjustment of various systems in the body. As the fall of Hb is very gradual, the onset of symptoms is insidious. Initially, pallor (**Fig. 4**) noticed over tongue, lips, conjunctiva, palms, nails, etc., easy fatigability, anorexia and irritability may be noticed.

Hyperdynamic circulation may lead to palpitations, shortness of breath, decreased exercise tolerance and congestive heart failure. Mild degree of hepatosplenomegaly is also not uncommon. Pedal

Table 3 Prevalence of anemia among children aged 6–35 months (%), India

Anemia level	NFHS-2			NFHS-3		
	Urban	Rural	Total	Urban	Rural	Total
Mild (10.0–10.9 g/dL)	23.7	22.7	22.9	25.8	25.7	25.7
Moderate (7.0–9.9 g/dL)	42.0	47.1	45.9	42.0	51.7	49.4
Severe (< 7.0 g/dL)	5.1	5.5	5.4	4.4	3.5	3.7
Any anemia (< 11.0 g/dL)	70.8	75.3	74.3	72.2	80.9	78.9

NFHS—National Family Health Survey

Table 4 Prevalence of anemia in children in India (nationwide large survey)

Background characteristics	Percentage of children with levels of anemia		Percentage of children with any anemia	Number of children
	Severe	Moderate or Severe		
Residence				
Rural	3.0	49.1	96.9	141,483
Urban	2.7	44.9	96.6	51,887
Sex of the child				
Male	3.0	47.3	96.7	100,958
Female	2.9	48.7	97.0	92,364
Age of child (Months)				
0–11	3.9	58.3	97.6	26,401
12–23	4.1	61.3	98.1	29,607
24–47	3.2	49.6	97.2	66,455
48–71	1.9	36.9	95.7	70,907

Source: Computed from DLHS-RCH, 2002 Survey date files



Figure 4 Pallor of the palm

edema in IDA may be due to congestive heart failure, impaired renal function or associated protein deficiency. Rarely increased intracranial tension with papilledema may occur. Skull changes with caput quadratum appearance (frontoparietal bossing) similar to that seen in congenital hemolytic anemia may be seen in children with chronic long-standing iron deficiency occurring since early life. These skeletal changes do not reverse with iron therapy.

Nonhematologic Consequences of Iron Deficiency

It has been shown that iron deficiency per se even in the absence of anemia leads to several morphological and biochemical changes at tissue level with deleterious effects on various systems.

Koilonychia and platynychia (**Fig. 5**), glossitis, stomatitis, and angular cheilosis are the other common features, not commonly seen in children. Formation of mucosal webs at the pharyngoesophageal junction causes dysphagia mainly for solids. The triad of dysphagia due to esophageal webs, koilonychia and splenomegaly in a patient with IDA is known as the Plummer-Vinson or Patterson-Kelly syndrome.

Pica is a well-documented feature of anemia in children. Craving to eat unusual substances such as dirt, clay (geophagia), ice (pagophagia), laundry starch (amylphagia), salt, cardboard, etc., is seen in almost 70–80% of patients and is usually cured by prompt iron therapy.

Functional impairments of various tissues such as the myocardium, peripheral nerves, intestinal mucosa, cerebral cortex, kidney and liver, etc., have been demonstrated in patients of iron deficiency, which have been corrected by iron therapy before a significant rise in the Hb level.

There are studies to suggest that children with iron deficiency have lower intelligence quotient (IQ) scores, lack of concentration, distractibility, short attention span and impaired mental and motor development. These changes lead to scholastic backwardness too and may be irreversible if the onset is in infancy.

Iron deficiency also adversely affects the immune system, thus increasing susceptibility to infection. Another area of special significance is poor endurance and physical fitness even with mild anemia, probably due to lower myoglobin production.

INVESTIGATIONS

Complete Blood Count and Peripheral Smear

There is low Hb/low hematocrit (Hct) with reduced red cell count; red cell indices may not be altered in mild IDA, however, with ongoing



Figure 5 Koilonychia in iron deficiency anemia

deficiency, these are reduced as follows: mean corpuscular volume (MCV) less than 80 fL, mean corpuscular hemoglobin (MCH) less than 27 pg and mean corpuscular hemoglobin concentration (MCHC) less than 32%, increased red cell distribution width (RDW) [$> 14\%$ by coefficient of variation (CV)] (normal $13.4 \pm 1.2\%$); white cell counts are normal, and platelet count may be increased or normal. Peripheral smear shows microcytic, hypochromic anemia with significant anisocytosis and poikilocytosis (**Fig. 6**).

Serum Iron Studies

Normal serum iron level varies considerably. It has a diurnal variation with a peak in the morning and trough in the evening. Dietary intake also can alter the iron levels in the plasma and hence they are unreliable by themselves. Serum iron concentration may also be affected by chronic infection, malignancies and chemotherapy as well as iron medication. Values below 40 $\mu\text{g/dL}$ are considered significantly low and suggestive of iron deficiency (in absence of infection or other disorders which affect iron metabolism).

Total Iron Binding Capacity and Transferrin Saturation

Total iron binding capacity (TIBC) is the measure of plasma transferrin, which is free, not bound to iron. The normal value of TIBC is 250–350 $\mu\text{g/dL}$. In iron deficiency states, TIBC is

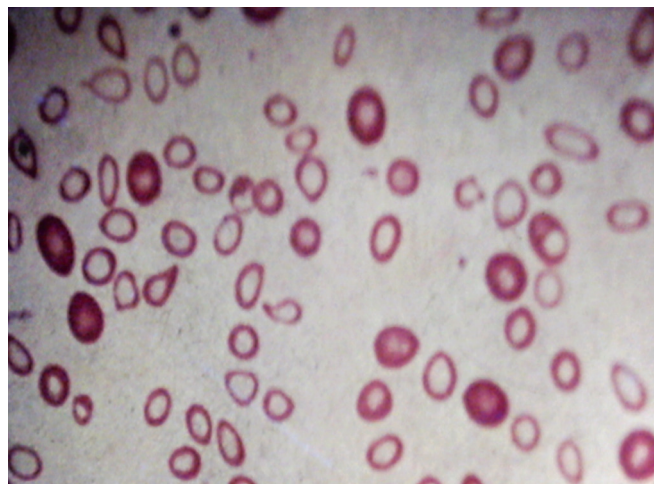


Figure 6 Peripheral blood smear with hypochromic, microcytic red cells with anisocytosis and poikilocytosis in iron deficiency anemia

increased ($> 350 \mu\text{g/dL}$) and transferrin saturation (TS) is reduced to below 16% ($< 12\%$ for children). TIBC less than $200 \mu\text{g/dL}$ is characteristic of inflammatory disease. Factors that affect serum iron concentration do not alter values of TIBC.

Serum Ferritin

Serum ferritin is a sensitive laboratory index of iron status. It is the best noninvasive test (gold standard with a high specificity and adequate sensitivity) for evaluating iron status in the body. A serum ferritin value of less than 12 ng/mL is highly specific for iron deficiency, but gives no information about its magnitude. Serum ferritin is increased in chronic disorders, e.g., chronic infection and inflammation, malignancies, chronic liver disorders. In presence of any of these, a coexisting IDA can be missed.

Soluble Plasma Transferrin Receptor

In IDA, transferrin receptors (TfRs) are increased due to an increased turnover associated with ineffective erythropoiesis and, an increase in cellular TfR expression produced by iron starvation. Unlike the serum ferritin, which only identifies iron deficiency, the serum TfRs measure its severity.

Content of Hemoglobin in Reticulocytes

Content of Hb in reticulocytes (CHR) at a cut-off of 27.5 pg has a sensitivity of 83% and a specificity of 72% for diagnosis of IDA and can be used as a corroborative investigation.

Bone Marrow Examination

Bone marrow aspiration is not recommended for the diagnosis of IDA, as there are simpler, noninvasive and relatively inexpensive tests, which diagnosis of IDA. In contrast, bone marrow iron staining, though a gold standard, is very painful, expensive and cumbersome to perform. However, bone marrow when done shows increased cellularity with micronormoblastic erythroid hyperplasia. On staining with Prussian blue (Perls' reaction), there is little or no stainable iron seen.

TREATMENT

Basic principles of management include correction of anemia and treatment of underlying cause. Treatment of IDA depends upon the severity and associated complications. Those with very severe anemia and/or congestive heart failure, with Hb less than 5 g/dL require hospitalization. Oral iron therapy with monitoring is adequate for those without evidence of congestive heart failure. Packed red cell transfusion is required for those in congestive heart failure irrespective of the level of Hb. Packed red cells at 5 mL/kg should be slowly administered over 2–3 hours to avoid volume overload.

Medicinal Iron Therapy

Oral iron therapy is the ideal treatment for IDA. It is safe, economical and as effective as parenteral therapy. For infants and children, the recommended therapeutic dose is 3–6 mg of elemental iron/kg body weight/day. Higher doses are unnecessary and may increase side effects, reducing patient compliance. Although the desired Hb level is usually reached in 2–3 months, iron therapy should continue for another 2–3 months to build up iron stores.

Ferrous compounds are better absorbed than ferric iron, and are therefore the recommended form of iron for treatment. Amongst ferrous compounds, ferrous sulfate (20% elemental iron), gluconate (30% elemental iron) and fumarate (33% elemental iron) compounds are the most commonly used preparations. A ferrous sulfate preparation microencapsulated with phospholipids was found to have equivalent bioavailability

to ferrous sulfate. Other ferrous compounds used include ferrous ascorbate, succinate, lactate, glycine sulfate, glutamate, citrate, tartrate and pyrophosphate. Ferrous salts have a high incidence of gastrointestinal (GI) side effects ($\sim 23\%$).

The ferric compounds offer no additional advantage over ferrous fumarate, gluconate or sulfate and are more expensive. Ferric ammonium citrate (18% elemental iron) is the most commonly used of these salts. There has been no significant difference demonstrated in the toxicity profile of ferrous and ferric compounds.

Iron amino acid chelates are conjugates of the ferrous or ferric ion with amino acids. Although numerous conjugates have been formulated the most studied of these are ferrous bis-glycinate (20% elemental iron content), ferric tris-glycinate and ferrous glycine sulfate. They have no effect on the color or taste of food products. Comparison of ferrous sulfate with ferrous bis-glycinate in infants of 6–36 months of age showed equivalent rise in Hb in the two groups.

Iron polymaltose complex (IPC) is a novel iron preparation, which contains nonionic iron and polymaltose in a stable complex. IPC compounds have, however, not been found to be as efficacious as the traditional ferrous compounds in the treatment of IDA.

Carbonyl iron is a small particle preparation of highly purified metallic iron. This preparation has been found to be variably effective and safe in prevention and treatment of iron deficiency with lesser side effects compared to ferrous sulfate. Carbonyl iron is much less toxic than other ionized forms of iron.

Colloidal iron is a readily available iron preparation; however, there is hardly any data on colloidal iron. Iron acetyl transferrin in infants has been shown to be efficacious for treatment of IDA. Iron protein succinylate is another compound which has been tried in children in some studies and has been found more efficacious than IPC preparations. Iron in the form of Hb has little advantage over other iron preparations, and fails to provide the daily therapeutic requirement in the recommended doses. Large volumes need to be ingested to produce therapeutic effect.

Folic acid can be combined with iron at negligible extra cost. Addition of vitamin C (200 mg) increases the absorption of iron by about 30%. But addition of vitamin C may add to the cost significantly. Vitamin B_{12} may need to be given in nonresponders or with evidence of megaloblastic anemia.

Uncoated or sugar-coated tablets are not only cheapest but also disintegrate easily in stomach. However, they are oxidized in humid environment, making the compound less stable. Enteric-coated tablets are more expensive and may not disintegrate in the stomach, and hence absorption may not be adequate. In slow release preparations, only a small amount of iron comes into contact with the duodenal mucosa at a given time, thus improving absorption and reducing GI side effects. Though liquid preparations are very useful in children, but they deteriorate on storage.

In 1996, a group of consultants from the United Nations Children's Fund (UNICEF) devised a new technology called *sprinkles* through which encapsulated micronutrients in powder form could be added directly to food at the household level. The micronutrients are encapsulated in a thin coating of a soy-based hydrogenated lipid, which prevents the micronutrients from oxidizing the food. Thus, the color or taste of food to which sprinkles are added does not change. The encapsulated micronutrients are packaged in single-dose sachets to ensure that the correct amount of iron is given. The contents of the sachets are then sprinkled onto whatever food is served in the household, including typical complementary and family foods. This has been useful both for treatment and prevention of IDA. As the iron in *sprinkles* is microencapsulated, other micronutrients, such as vitamin A, folic acid, vitamin B_{12} and ascorbic acid, can be included without significant loss of nutrient stability.

Side Effects

Side effects are mild and have been reported in about 14% of patients and not related to any particular iron compound. Intolerance to oral iron is basically related to the amount of iron in the gut. Usual side effects are nausea, vomiting, constipation, diarrhea, and abdominal discomfort. Iron absorption is maximum during the initial phase of therapy and is inversely proportionate to the level of Hb. It declines from 14% in the 1st week to 7% in the 4th week to 2% after 4 months.

Parenteral Iron Therapy

Parenteral route should be used only in definite indications like severe intolerance to oral iron, GI bleeding aggravated by oral iron therapy, bleeding more than the increase in Hb with oral iron, preoperative in urgent surgeries, and malabsorption syndromes.

There is no evidence that the rate of Hb response is different in oral or parenteral therapy. Iron dextran complex was the most commonly used preparation in the past. However, with availability of the newer preparations with much lesser side effects, (such as ferric carboxymaltose, sodium iron gluconate, ferumoxytol and iron sucrose). Iron dextran is no longer the first choice for parenteral therapy. Experience with the newer compounds has been encouraging, though ferric carboxymaltose is not yet approved for use in children. The total dose required may be calculated using one of the following formulae:

$$\text{Iron (mg)} = \text{Weight (kg)} \times \text{Hb deficit (g/dL)} \times 80/100 \times 3.4 \times 1.5$$

Or

$$\text{Weight (kg)} \times \text{Hb deficit (g/dL)} \times 4$$

The response can be predicted. Adverse reactions include skin rash, arthralgia, myalgia, and rarely anaphylaxis.

Response to Therapy

In uncomplicated IDA, administration of iron shows a predictable reticulocytosis and a rise in Hb. Hb concentration remains the most dominant predictor of response to therapy in uncomplicated iron deficiency. A positive response to therapy can be defined as a daily increase in Hb concentration of 0.1 g/dL (0.3% or 1% rise in Hct) from the 4th day onwards. Lower the initial Hb greater is the rise in the Hb following iron therapy. A reticulocyte response is generally seen in 7–10 days whereas a very early rise is observed in CHR (within 2–4 days).

Effect of Maternal Iron Deficiency on Fetus and Infant

It has been adequately shown through extensive studies that mild maternal anemia due to iron deficiency does not compromise the Hb levels in the fetus or newborn, though it reduces the storage iron. However, severe IDA in the pregnant woman definitely causes significant adverse effects in the unborn fetus as well as in the newborn. It leads to lower Hb as well as lower ferritin. It may cause placental insufficiency, prematurity, low birthweight, asphyxia, subnormal brain development, etc. Addressing the iron deficiency state of the adolescent girl who is the future pregnant and lactating woman is crucial to have an iron replete future population too!

PREVENTION

Food-based approach constitutes the most desirable and sustainable method of preventing iron deficiency. Supplementation of iron should be done in vulnerable age

groups including pregnant women, toddlers, adolescent girls, etc. Once the child has been weaned, dietary modification can help to increase iron intake through iron-rich foods. Avoid limiting factors—the poor bioavailability of iron due to presence of inhibitors like phytates in cereal-based diet and phenolic compounds including tannin present in tea and coffee. Absorption promoter of iron like vitamin C has been shown to be deficient in Indian diet. Therefore, inclusion of vitamin C containing diet prevents iron deficiency. Fruits (uncooked as heat destroys vitamin C) with lunch and dinner for 1 month have shown to raise Hb level by 2.2 g/dL. Fermentation and germination can enhance iron absorption by increasing vitamin C content and lowering phytic acid content. Heme iron present in meat is not only better absorbed, but increases absorption of nonheme iron of vegetable foods. Fortification of foods with iron is a cost effective, long-term measure for improving the iron status of the entire population. Using sprinkles in routine food preparations is a feasible option. A formula for double-fortified salt, i.e., salt fortified with iodine and iron has been developed and which was found to be effective in controlling nutritional anemia.

IN A NUTSHELL

1. Iron deficiency anemia is the most common nutritional deficiency and occurs primarily due to poor intake of iron or diet having low iron content.
2. Various factors which affect iron absorption have been reviewed.
3. Iron metabolism has been described in simplified way for better understanding.
4. Iron deficiency anemia has many adverse effects.
5. It can be managed with iron supplementation.
6. Correction of underlying factors is important to prevent recurrence of IDA.
7. Iron deficiency anemia can be prevented by fortification of food items.

MORE ON THIS TOPIC

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Chapter 38.7

Megaloblastic Anemia

Sangeeta Mudaliar, Bharat Agarwal

Megaloblastic anemia is characterized by the presence of macrocytes in the blood and megaloblasts in the bone marrow. The common causes of megaloblastic anemia in childhood are folate or vitamin B₁₂ [cobalamin (Cbl)] deficiency or defects in their metabolism. Deficiencies of thiamine, ascorbic acid and tocopherol may also be related to megaloblastic anemia.

EPIDEMIOLOGY

In tropical and subtropical regions like South Asia, Mexico, Africa, Central and South America, nutritional megaloblastic anemia is more prevalent. In these populations, it is commonly seen in age group of 3–18 months and is associated with prolonged breastfeeding and maternal deficiencies.

Over the last three decades, due to dietary supplementation during pregnancy to prevent neural tube defects, the prevalence of folate deficiency has fallen to 2–10% from 70% to 75%. Cbl deficiency is now emerging as a significant cause of nutritional megaloblastic anemia.

ETIOLOGY

Tables 1 to 3 enlist the causes of megaloblastic anemia, vitamin B₁₂ deficiency and folate deficiency, respectively.

Folate Deficiency

Exclusive goat milk feeding can cause megaloblastic anemia due to lack of folate in goat milk. Maternal folate deficiency with prolonged breastfeeding is another important causative factor in infants. Ascorbate (vitamin C) is important to preserve intrinsic folates from dietary sources. Vitamin C deficiencies have been reported to be associated with folate deficiency. In conditions with increased cell turnover such as leukemia, chronic hemolytic anemia and sideroblastic anemia, there is increased demand which if unmet leads to folate deficiency anemia.

Impaired absorption as in tropical sprue, gluten enteropathy and other intractable diarrheas leads to folate deficiency. Relative folate deficiency is caused by induction of microsomal enzyme in folate metabolism. When used on a long-term basis sulfonamide antibiotics may interfere with folate metabolism causing megaloblastic changes. Antineoplastic agents such as methotrexate which are inhibitors of human dihydrofolate reductase (DHFR), also cause megaloblastic changes.

Hereditary folate malabsorption (congenital malabsorption of folate) may present in early infancy with megaloblastic anemia, mouth ulcers, failure to thrive, chronic or recurrent diarrhea, seizures, and progressive neurological deterioration. Low red cell, serum and cerebrospinal fluid folate levels with classic clinical features are diagnostic. It is a rare disease, with autosomal recessive inheritance.

Methylenetetrahydrofolate reductase deficiency is rare and may present as severe form in first few months of life or as late as 16 years of age in a much milder form. Megaloblastic anemia is not common in these patients because reduced folates are available for purine and pyrimidine synthesis. The most common presentation is developmental delay. Other features may be motor and gait abnormalities, seizures, mental retardation, strokes, psychiatric manifestations, microcephaly and vasculopathy.

Vitamin B₁₂ Deficiency

Nutritional deficiency occurs in breastfed babies of B₁₂ deficient mothers and in strict vegans, and lacto vegetarians. Absorption of vitamin B₁₂ is impaired in congenital absence of intrinsic factor (IF), juvenile pernicious anemia, fish tapeworm infestation, postgastric surgery and ileal malabsorptive states. Therapy with para-aminosalicylic acid, colchicine and zidovudine may lead to B₁₂ deficiency. Inherited disorders like Imerslund-Gräsbeck syndrome (proteinuria with renal tubular defect), inborn errors of Cbl metabolism (methylmalonic aciduria, homocystinuria), and IF/Cbl receptor defect are rare disorders leading to B₁₂ deficiency.

VITAMIN B₁₂ TRANSPORT AND INBORN ERRORS OF METABOLISM

Transport Disorders

Food Cobalamin Malabsorption

The release of Cbl from the food in stomach is mediated by acidic pH and peptic activity. This release may be compromised in patients with impaired gastric function due to gastrectomy or atrophic gastritis. These patients have normal Schilling test but low serum Cbl and mild elevated methylmalonic acid and homocysteine.

Intrinsic Factor Deficiency

This form of pernicious anemia resulting either due to production of immunologically active but nonfunctional IF or total lack of IF production is autosomal recessively inherited. Clinical features include megaloblastic anemia, developmental delay and myelopathy. It usually presents in early childhood after the first year of life, but may not appear until adolescence or adulthood. These patients have normal gastric cytology and gastric acid secretion. Absorption of Cbl is abnormal in these patients but gets normalized when the vitamin is mixed with a source of normal IF.

Imerslund-Gräsbeck Syndrome (Defective Vitamin B₁₂ Transport by Enterocytes)

Imerslund-Gräsbeck syndrome causes clinical manifestations of vitamin B₁₂ deficiency usually within the first 2 years, later presentation may also occur in some. Clinical features include pallor, weakness, anorexia, failure to thrive and recurrent infections. They also have proteinuria of tubular type as a common feature. These

Table 1 Causes of megaloblastic anemia

Congenital	Acquired
Oroticaciduria	Leukemia
Thiamine responsive megaloblastic anemia (DIDMOAD)	Aplastic anemia
Lesch-Nyhan syndrome	Liver pathology
Associated with congenital dyserythropoietic anemia	Refractory megaloblastic anemia
Congenital familial megaloblastic anemia	Sideroblastic anemias
Drug-induced	
• Inhibitors of ribonucleotide reductase (hydroxyurea, cytosine arabinoside)	
• Purine analogs (e.g., 6-mercaptopurine, thioguanine and azathioprine)	
• Pyrimidine analogs (6-azauridine, 5-fluorouracil)	

Table 2 Causes of vitamin B₁₂ deficiency

<i>Inadequate intake</i> <ul style="list-style-type: none"> • <i>Dietary:</i> Food fads, veganism, malnutrition • Maternal deficiency causing B₁₂ deficiency in breastmilk <i>Defective absorption</i>	
Failure to secrete intrinsic factor <ul style="list-style-type: none"> • Congenital deficiency of intrinsic factor (normal gastric mucosa) <ul style="list-style-type: none"> – Quantitative – Qualitative (biologically inert) • Juvenile pernicious anemia associated with <ul style="list-style-type: none"> – IgA deficiency – Gastric atrophy (autoimmune) – Gastric autoantibodies and autoimmune polyendocrinopathies • Gastric mucosal disease <ul style="list-style-type: none"> – Gastrectomy – Corrosives 	Failure of absorption in small intestine <ul style="list-style-type: none"> • Malabsorption of vitamin B₁₂ <ul style="list-style-type: none"> – Abnormal intrinsic factor – Imerslund-Gräsbeck syndrome – Chelating agents which bind calcium and interfere with absorption of vitamin B₁₂ (EDTA, phytates) • Generalized malabsorption disorders <ul style="list-style-type: none"> – Intestinal resection – Gluten enteropathy – Crohn's disease – Zollinger-Ellison syndrome – Tuberculosis of terminal ileum – Prolonged use of medication which decreases gastric acidity – Pancreatic insufficiency • Competition for vitamin B₁₂ <ul style="list-style-type: none"> – Small bowel bacterial overgrowth – <i>Giardia lamblia</i>, <i>Diphyllobothrium latum</i>, <i>Strongyloides stercoralis</i>
<i>Transport defect of vitamin B₁₂</i> <ul style="list-style-type: none"> • Partial deficiency of transcobalamin I (TC I) (R-binder deficiency) • Deficiency of TC II <i>Vitamin B₁₂ metabolism defects</i>	
Congenital <ul style="list-style-type: none"> • Adenosylcobalamin deficiency CblA and CblB diseases • Deficiency of methylmalonyl-CoA mutase • Methylcobalamin deficiency CblE and CblG diseases 	Acquired <ul style="list-style-type: none"> • Hepatic pathology • Protein energy malnutrition • Drugs affecting absorption and/or utilization of vitamin B₁₂ (e.g., <i>p</i>-aminosalicylic acid, ethanol, colchicines, neomycin)
<ul style="list-style-type: none"> • <i>Combined adenosylcobalamin and methylcobalamin deficiencies:</i> CblC 	

Table 3 Causes of folate deficiency

<i>Inadequate intake</i> <ul style="list-style-type: none"> • Poverty, food fads, ignorance • Malnutrition • Goat's milk • Sustained boiling loses up to 50–95% folate • Prematurity • Post bone marrow transplantation (heat-sterilized food) 	
<i>Increased requirements</i> <ul style="list-style-type: none"> • Chronic hemolytic anemia with ineffective erythropoiesis (e.g., thalassemia major) • Rapid growth (e.g., prematurity, pregnancy) • Dyserythropoietic anemias • Hypermetabolic states (e.g., hyperthyroidism, infection) • Malignant disease (e.g., lymphoma, leukemia) • Extensive skin disease (e.g., psoriasis, dermatitis herpetiformis, exfoliative dermatitis) • Cirrhosis • Post bone marrow transplant (regeneration of bone marrow and epithelial cell) 	
<i>Disorders of metabolism</i>	
Congenital (enzyme deficiencies) <ul style="list-style-type: none"> • Methylenetetrahydrofolate reductase • Glutamate formiminotransferase • <i>Functional N⁵-methyltetrahydrofolate:</i> Homocysteine methyltransferase • Dihydrofolate reductase • Methenyltetrahydrofolate cyclohydrolase • <i>Primary methyltetrahydrofolate:</i> Homocysteine methyltransferase 	Acquired <ul style="list-style-type: none"> • Defective utilization of folate • Drugs—methotrexate, pentamidine trimethoprim, pyrimethamine • Vitamin B₁₂ deficiency • Hepatic pathology • Alcohol abuse

Excess excretion, e.g., vitamin B₁₂ deficiency, chronic dialysis, hepatic disorder.

patients have normal intestinal morphology and normal IF. There is no evidence of antibodies to IF. Their selective defect in vitamin B₁₂ absorption does not correct by treatment with IF. Treatment with systemic vitamin B₁₂ corrects the anemia but not the proteinuria.

Partial Deficiency of Transcobalamin I (R-Binder or Haptocorrin Deficiency)

Partial deficiency of transcobalamin I (TC I) with TC I concentrations of 25–54% of the mean normal concentration has been reported. Clinically this syndrome is characterized by a myelopathy not explained by any other cause. Though serum vitamin B₁₂ concentrations are persistently low but patients are asymptomatic of vitamin B₁₂ deficiency since they have normal TC II-Cbl levels.

Transcobalamin II Deficiency

Transcobalamin II deficiency is a rare autosomal recessive disorder. The defect in TC II may be due to lack of protein causing an inability to bind or facilitate uptake of Cbl into cells. The Schilling test is usually abnormal in these patients suggesting that the TC II molecule may play a role in the transport of Cbl across the ileal cell mediated by IF.

Severe megaloblastic anemia occurs usually in the first few months of life. Other symptoms include diarrhea, weakness and failure to thrive. Some patients may present with isolated erythroid hypoplasia or decreased production of all the hematopoietic cell lines. Untreated or undertreated patients may present with neurologic symptoms later in life. And despite adequate treatment, neurologic deficits persist. Severe immunologic deficiency with defective humoral and cellular immunity has been reported.

Laboratory findings show hyperhomocysteinemia, macrocytic anemia, and raised methylmalonic acid levels.

Disorders of Metabolism

Acquired

Impaired utilization of Cbl occurs in protein energy malnutrition and hepatic dysfunction. Few drugs like colchicine, neomycin, ethanol, etc. are associated with defective absorption or utilization of vitamin B₁₂.

Congenital

All the congenital defects of Cbl metabolism are autosomal recessively inherited. The patients may have either methylmalonic acidemia or hyperhomocysteinemia or both. Methylmalonic acidemia results from defective mitochondrial methylmalonyl-CoA mutase or its cofactor adenosylcobalamin. Hyperhomocysteinemia occurs as a result of abnormality in the cytoplasmic methionine synthase or its cofactor methylcobalamin.

Patients have severe metabolic acidosis and large amounts of methylmalonic acid in urine, cerebrospinal fluid and blood.

Adenosylcobalamin Deficiency: CblA and CblB Diseases

Cells in these patients fail to synthesize adenosylcobalamin. Deficiency of a mitochondrial nicotinamide adenine dinucleotide phosphate (NADPH)-linked aquacobalamin reductase results in CblA disease. In CblB, final step in adenosylcobalamin synthesis is affected due to defect in adenosyltransferase.

These defects in turn cause impaired methylmalonyl-CoA mutase activity resulting in to methylmalonic acidemia.

Infants present in the first few weeks or months of life with severe ketoacidosis, hypoglycemia and hyperglycinemia. Ketoacidosis results in developmental delays and failure to thrive. With the relief of ketoacidosis, normal growth ensues. Serum Cbl levels are normal.

Deficiency of Methylmalonyl-CoA Mutase

Life threatening or fatal ketoacidosis may occur due to defects in methylmalonyl-CoA mutase apoenzyme. It results in methylmalonic aciduria. Symptoms include failure to thrive, lethargy, muscular hypotonia, respiratory distress, vomiting and dehydration. High levels of ammonia, glycine and ketones in the blood and urine may be present. Many also have hypoglycemia, low WBC and platelets. This defect does not respond to vitamin B₁₂ therapy. On a protein diet, the symptoms get rapidly induced.

Methylcobalamin Synthesis Deficiency: CblE and CblG Diseases

Functional methionine synthase deficiency (CblE, CblG) is characterized by homocystinuria and hypomethioninemia without methylmalonic aciduria. Usually symptoms like megaloblastic anemia, developmental delay, ataxia, cerebral atrophy, EEG changes, tone abnormalities, seizures, blindness, nystagmus and failure to thrive occur within the first 2 years of life, but a few patients have been diagnosed in adulthood.

Combined Adenosylcobalamin and Methylcobalamin Deficiency: CblC, CblD, and CblF Diseases

In these disorders, failure to synthesize both adenosylcobalamin (resulting in methylmalonic aciduria) and methylcobalamin (resulting in hypomethioninemia and homocystinuria) occurs resulting in deficient activity of methylmalonyl-CoA mutase and N⁵-methyltetrahydrofolate (N⁵-MTHF): homocysteine methyltransferase.

In CblF, the exit of Cbl from the lysosome is defective while in CblC and CblD, the defect is in Cbl reductase. These patients are symptomatic in the first year of life. Clinical features include poor feeding, failure to thrive, lethargy, megaloblastic anemia, spasticity, psychosis, developmental retardation. Usually it is fatal in patients who present in the first month of life. Those who present later have a better prognosis. Chorionic villus biopsy can help in prenatal diagnosis in CblC disease.

Other Inherited Disorders with Megaloblastic Anemia

- Diabetes insipidus, diabetes mellitus, optic atrophy, deafness (DIDMOAD) syndrome (thiamine responsive)
- Refractory sideroblastic anemia
- Congenital disorders of DNA synthesis
- Orotic aciduria
- Lesch-Nyhan syndrome.

Thiamine-Responsive Megaloblastic Anemia

Diabetes insipidus, diabetes mellitus, optic atrophy, deafness (DIDMOAD) syndrome is a rare autosomal recessive disorder. The characteristic features are diabetes mellitus, diabetes insipidus, sensorineural deafness and megaloblastic anemia which respond to pharmacologic doses of thiamine. Additional clinical findings include optic atrophy, cardiomyopathy, and stroke like episodes.

Orotic Aciduria

Orotic aciduria is an autosomal recessive defect of pyrimidine synthesis which results from defective conversion of orotic acid to uridine. Large amount of orotic acid is excreted in the urine. It is associated with severe megaloblastic anemia, neutropenia, failure to thrive and physical and mental retardation.

Lesch-Nyhan Syndrome

In this disorder, purine synthesis is impaired due to lack of hypoxanthine phosphoribosyltransferase. Clinical characteristics

include mental retardation, self-mutilation and choreoathetosis. Megaloblastic anemia is present in some patients.

PATHOPHYSIOLOGY

Folate Deficiency

Folate and B₁₂ deficiency and defect in their metabolism result in defective DNA synthesis resulting in megaloblastic anemia. The first phase in the absorption of natural folates involves digestion of polyglutamates to monoglutamates. Absorption of folates occurs in the small intestine through a saturable carrier process for relatively low intestinal concentrations of folate and by diffusion for high concentrations of folate.

Folic acid is essential for purine biosynthesis. Folic acid absorbed from the diet gets activated to produce active tetrahydrofolic acid (THF). THF is necessary for single carbon transfers in the synthesis of pyrimidine nucleotides. With less amount of biologically active THF, the ability to repair and replicate DNA is decreased. Vitamin B₁₂ is a cofactor for the activation of folic acid in a step that also converts homocysteine to methionine.

In folate deficiency, THF production is depleted causing slowing of DNA synthesis. This results in pancytopenia due to defective hematopoiesis. The cells that are produced have immature nuclei compared with the degree of maturation of the cytoplasm due to arrest of nuclear maturity.

Vitamin B₁₂ Deficiency

Cobalamin is synthesized by microorganisms and is present only in foods of animal origin (meat or fish) such as milk, dairy products, liver, muscle and eggs. It remains stable with cooking at high temperature but is inactivated by ascorbic acid.

In the acidic pH of stomach, Cbl is released by enzymatic digestion from protein complexes in food. It binds to R binder (haptocorrin) present in saliva and gastric juice (**Table 4**). After release from R binder in the duodenum by pancreatic proteases, Cbl binds to IF (synthesized by gastric parietal cells, it is a 45 kDa glycoprotein). In bile also Cbl is attached to R binder, it forms a complex with IF in the duodenum. The complex of IF-Cbl gets attached to the ileal brush border through its receptor cubilin. Usually a limited absorption of 1.5–2.5 µm of Cbl occurs through ileal receptors from a single meal; rarely larger amounts have also been documented. Also a small fraction (< 1%) of a large oral dose gets absorbed passively from the oral, gastric and small intestinal mucosa. The IF-Cbl complex is digested within the enterocyte and the Cbl appears in portal blood attached to TC II (a 38 kDa polypeptide). The Cbl-TC II complex has a rapid metabolic turnover with a half-life of about 6 min. Cbl can bind to either TC I or TC II in the plasma.

Cobalamins are stored in tissues in its coenzyme forms. One-third of body stores are found in the liver. Because of well stored Cbls in tissues, it takes time for deficiency to manifest. Cbl acts

as a coenzyme in propionic acid metabolism for conversion of methylmalonyl-CoA and in the synthesis of methionine from homocysteine. Synthesis of methionine from homocysteine also requires a folate coenzyme N⁵-MTHF.

In vitamin B₁₂ deficiency, propionic acid metabolism is slowed resulting in accumulation of methylmalonic acid. Also in vitamin B₁₂ deficiency folate becomes trapped in its methyl form causing a deficient synthesis of methylene THF. Methylene THF is a coenzyme for thymidyl acid synthesis. Thus, the folate trap occurring as a result of deficiency vitamin B₁₂, slows down DNA synthesis.

CLINICAL FEATURES

Older children present with pallor, easy fatigability, irritability and lethargy. Infants may have regression of milestones and infantile tremor syndrome. On examination, most patients have pallor and sallow yellow complexion. They may have hyperpigmentation of knuckles and nail bed. Patients with pernicious anemia present with anemia, diarrhea, paresthesia, anorexia, recurrent glossitis, and neuropsychiatric symptoms. Vitamin B₁₂ deficiency frequently affects vibratory sensation in the extremities. These changes reflect neurotoxicity occurring because of deficient B₁₂ levels. Once the child is B₁₂ replete, these symptoms can be monitored to determine the degree of resolution.

APPROACH TO DIAGNOSIS

A careful and detailed dietary history is important to diagnose megaloblastic anemia. Dietary faddism, family-induced dietary restriction, exclusive goat's milk should be enquired for. In the case of a breastfed infant with megaloblastic anemia, the maternal dietary history should also be obtained. In infants, dietary vitamin B₁₂ deficiency is quite rare, it may occur in breastfed infants whose mothers are B₁₂ deficient. A careful history of the mother's diet, including the current diet, her diet during and before pregnancy is extremely important.

Document the presence or absence of sprue, malabsorption syndromes and conditions such as intestinal blind-loop syndrome or bowel resection, Crohn's disease, or tuberculosis as potential causes of B₁₂ malabsorption. History of surgery involving the stomach, jejunum, or ileum is important as these may lead to megaloblastic anemia due to impaired absorption of B₁₂. Also, evaluate for other acquired disorders like parasitic infestation.

Leukemia and other malignancies should be ruled out if bone and joint pain are present; marrow replacement may cause pancytopenia in these patients. Bleeding and bruising may rarely be observed due to thrombocytopenia associated with vitamin B₁₂ deficiency; these symptoms should also raise suspicion of leukemia or other marrow replacement disorders.

Careful drug history is important. History of sulfa exposure or use of chemotherapeutic agents, such as methotrexate or azathioprine, anticonvulsants should be considered. Obtaining detailed family history and enquiring about members of extended family is necessary to detect congenital absence or deficiency of carrier proteins which is a common cause of vitamin B₁₂ deficiency occurring in families. These conditions often manifest during infancy and early childhood. Evaluate for Imerslund-Gräsbeck syndrome of proteinuria and excretion of Cbl and IF where appropriate.

Differential Diagnosis

Aplastic anemia, leukemia, myelodysplastic syndrome, malabsorptive diseases and lymphoproliferative states may present with macrocytosis, megaloblastoid marrow anomalies, pancytopenia or high-serum lactate dehydrogenase (LDH) and thus need to be differentiated from megaloblastic anemia.

Table 4 Steps in absorption of cobalamin

1. Release of food-bound cobalamin (in stomach)
↓
2. Binds to R binder (in stomach)
↓
3. Released from R binder (in the proximal small intestine)
↓
4. Binds to intrinsic factor (IF)—produced by gastric parietal cells
↓
5. Transport of IF-cobalamin complex intracellularly through the cubilin receptor (in the ileum)
↓
6. Bound to transcobalamin II (released into plasma)

INVESTIGATIONS

The goal is to confirm the diagnosis of megaloblastic anemia, distinguish between folate or Cbl or combined deficiency, and to determine the underlying cause—dietary, sociocultural or disease related.

Peripheral Blood Examination

There is anemia with low reticulocyte count and macrocytosis [mean corpuscular volume (MCV) 110–130 fL]. In presence of concurrent iron deficiency or thalassemia trait, macrocytosis may get masked. Hypersegmented neutrophils (defined as the presence of one or more six-lobed neutrophils or five or more neutrophils with five well-separated lobes among 100 segmented neutrophils) (**Fig. 1**) are present. There is leukopenia or normal WBC and platelet counts may be reduced.

Bone Marrow Examination

Bone marrow evaluation should be considered for any child with more than one abnormal cell line. It can help to rule out other disorders such as aplastic anemia, leukemia and myelodysplasia. Bone marrow in patients with megaloblastic anemia demonstrates the RBC precursor nuclear/cytoplasmic asynchrony and abnormal granulocyte precursors.

Marrow is hypercellular, myeloid:erythroid ratio changing from 3:1 to 1:1 due to increased erythropoiesis. Megaloblastic erythropoiesis with intermediate and orthochromatic features with a sieve like nucleus and hemoglobinized cytoplasm and mitotic figures is seen (**Fig. 2**). Dyserythropoiesis is evidenced by nuclear remnants, bi- and trinucleated cells, Howell-Jolly

bodies and dying cells. Band cells and giant metamyelocytes are present. Megakaryocytes are either normal or increased with pseudohyperdiploidy.

Erythroid precursors have a normal DNA content with an elevated RNA content. Because of the increased RNA per unit of DNA erythroid precursors are larger than normal cells at the same level of maturation. The nuclear chromatin of the erythroid precursors appears loose giving the characteristic appearance of the megaloblast. There is asynchronicity in maturation of the nucleus and cytoplasm leading to nucleus appearing less mature than the cytoplasm.

Vitamin B₁₂ and Folate Assessment

Serum homocysteine and serum methylmalonic acid levels are useful in differentiating between folate and Cbl deficiency. In folate deficiency, only homocysteine is raised with normal methylmalonic acid levels while in Cbl deficiency, levels of both are significantly raised.

Methylmalonic acid and total homocysteine levels are sensitive indicators of vitamin B₁₂ deficiency and correlate with clinical abnormalities and therapeutic response. However, care should be taken in interpreting these results as they are not specific to vitamin B₁₂ deficiency.

Serum folate and cobalamin levels are easily available tests but have high-false positivity and negativity. Also, the levels normalize fairly rapidly with replacement therapy or even with normal hospital diet. For folate assessment, the RBC folate level is the best measure of metabolically active folate and includes 5-MTHF in the assay. Serum folate measures the circulating pool of folate but does not accurately reflect the amount of THF present in the tissues.

Serum vitamin B₁₂ level Normal values 200–800 pg/mL, vitamin B₁₂ deficiency levels less than 80 pg/mL.

Serum and red cell folate levels Red cell folate normal levels: 74–640 ng/mL; serum folate: normal levels: greater than 5–6 ng/mL; borderline: 3–5 ng/mL; low: less than 3 ng/mL.

Serum and Urine Assessment

Serum LDH is elevated to range of 2,000–5,000 IU/dL. It reflects increased turnover of cells in the marrow due to ineffective erythropoiesis. Measurement of IF and urine proteins, if possible, detects Imerslund-Gräsbeck syndrome. Serum chemistries allow assessment of protein loss and nutritional status. For excluding orotic aciduria, urinary excretion of orotic acid should be assessed. Schilling test and formiminoglutamic acid (FIGLU) test were used in the past to diagnose vitamin B₁₂ and folic acid deficiency. However, these tests are not used currently.

TREATMENT

Signs of heart failure should be carefully monitored in patients with severe anemia to avoid worsening of the cardiovascular status. Blood transfusion should be given very slowly. Successful treatment of patients with folate and Cbl deficiency involves replacement of the deficient vitamins, identification of the underlying cause and appropriate therapy for that, improvement of the diet and regular follow-ups to evaluate and monitor the patient's clinical status.

Folate Deficiency

With 100–200 µg folic acid per day, optimal response may be seen in most patients. With administration of high-dose folate, the hematologic features of Cbl deficiency may reverse, but the neurologic manifestations can progress. So, it is important to rule out Cbl deficiency before treating solely with folate.

The appetite improves and a sense of well-being returns within 1–2 days of the treatment. There is a fall in serum iron

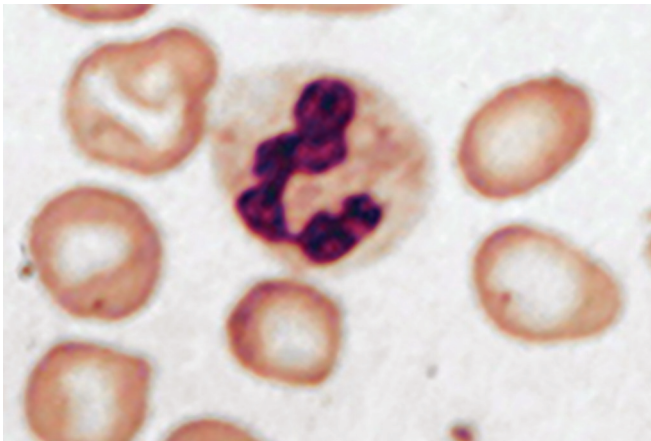


Figure 1 Hypersegmented neutrophil

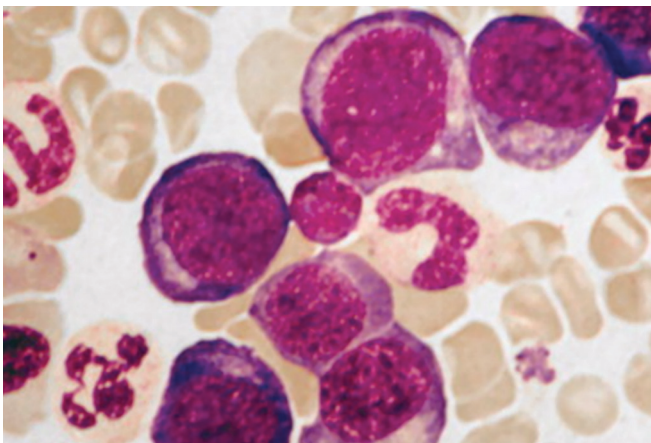


Figure 2 Bone marrow with megaloblast

in 24–48 hours and reticulocytes rise in 2–4 days with peak at 4–7 days. The hemoglobin levels become normal in 2–6 weeks. The WBCs and platelets increase with reticulocytes. Within the marrow, megaloblastic changes diminish in 24–48 hours, but large myelocytes, metamyelocytes, and band forms may be present for several days. Folic acid is usually given for several months till a new population of red cells has been formed. Folinic acid is used only for treating the toxic effects of DHFR inhibitors (e.g., pyrimethamine, methotrexate).

Etiology should be determined to prevent recurrence, for example, improved diet in nutritional deficiency, a gluten-free diet in gluten enteropathy, or treatment of underlying inflammatory disease such as Crohn's disease or tuberculosis. If the underlying disease is treated appropriately, there is no need to continue folic acid for life. In some situations, it is advisable to continue the folic acid to prevent recurrence, for example, in chronic hemolytic anemia such as thalassemia or in patients with malabsorption who do not respond to a gluten-free diet. Cases of hereditary DHFR deficiency respond to *N*5-formyltetrahydrofolic acid and not to folic acid.

For treating nutritional folate deficiency, an improved diet or a folate supplement, or both may be required. For patients who have folate malabsorption, 5–15 mg/day of folate should yield normal or high serum and erythrocyte folate levels.

Cobalamin Deficiency

Daily dose of 25–100 µg may be used to start therapy along with potassium supplements. Hypokalemia has been documented during B₁₂ initiation treatment in adults. In view of the ability of the body to store vitamin B₁₂ for long periods, monthly intramuscular (IM) injections in doses between 200 µg and 1,000 µg can be started as maintenance therapy. Lifelong treatment may be required in most cases of vitamin B₁₂ deficiency. Parenteral B₁₂ is needed for patients with defects affecting the intestinal absorption of vitamin B₁₂ (abnormalities of IF or of ileal uptake) to bypass the defective step.

Conventional therapy in megaloblastic anemia due to vitamin B₁₂ deficiency has been 1,000 µg of cyanoCbl or hydroxyCbl by injection daily for 1 week, followed by 100 µg of cyanoCbl weekly for 1 month and then monthly thereafter. Patients with complete TC II deficiency respond only to large amounts of vitamin B₁₂ and the serum Cbl level must be kept very high. Doses of 1,000 µg IM two or three times weekly are required to maintain adequate control.

Patients with methylmalonic aciduria with defects in the synthesis of Cbl coenzymes are likely to benefit from massive doses of vitamin B₁₂. These children may require 1–2 mg vitamin B₁₂ parenterally daily. However, not all patients in this group benefit from administration of vitamin B₁₂. Congenital methylmalonic aciduria can be diagnosed in utero by measurements of methylmalonate in amniotic fluid or maternal urine. It may be possible to treat vitamin B₁₂-responsive patients in utero.

In vitamin B₁₂-responsive megaloblastic anemia, the reticulocytes start to rise on the 3rd or 4th day, peak on the 6th to 8th day, and gradually fall to normal by about the 20th day. There is inverse relation between peak of the reticulocyte count and the degree of anemia. Bone marrow reversal from megaloblastic to normoblastic cells starts as early as 6 hours and is completed in 72 hours.

Permanent neurologic sequelae often occur. But, the level of alertness and responsiveness improves within 48 hours and developmental delays may catch up in several months in young infants. Prompt hematological responses occur with the use of oral folic acid, but it is contraindicated because it has no effect on

neurologic manifestations and may precipitate or accelerate the development of neurological symptoms.

OUTCOME

The degree of compliance with the treatment and the underlying cause predicts the outcome and prognosis of megaloblastic anemia. Folic acid deficiency is relatively easy to treat; added folate in the diet of the patients may be sufficient to treat. In some patients with vitamin B₁₂ deficiency, parenteral therapy may be necessary. Vitamin B₁₂ deficiency may be associated with severe neurologic abnormalities which may be long lasting and may not improve even with appropriate therapy.

IN A NUTSHELL

1. Megaloblastic anemia is characterized by the presence of macrocytes in the blood and megaloblasts in the bone marrow.
2. Common causes of megaloblastic anemia in childhood are deficiency of folate or vitamin B₁₂ (Cbl) or defects in their metabolism.
3. Impairment of DNA synthesis is the basic underlying pathogenetic mechanism resulting from deficiency of folic acid and/or vitamin B₁₂ at the cellular level.
4. Strict vegetarians and vegans are at high risk of vitamin B₁₂ deficiency.
5. Foliates are thermolabile and 50–95% loss may occur during cooking and boiling.
6. With appropriate investigations, underlying cause of the megaloblastic anemia should be established.
7. *Successful treatment of patients with folate and Cbl deficiency involves:* Correction of the deficiency, identifying and treating the causative disorder, improvement of the diet, follow-up evaluations to monitor the clinical status and to prevent the recurrences.

MORE ON THIS TOPIC

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Chapter 38.8

Approach to Hemolytic Anemia

VP Choudhry

Increased red cell destruction resulting in anemia is the hallmark of hemolytic anemia. Normal red blood cells (RBCs) survive for 100–200 days. RBC survival depends upon the severity of hemolytic process. RBC destruction secondary to intracorporeal (intrinsic) or extracorporeal (extrinsic) are the predominant causes for various hemolytic mechanisms. Hematopoietic system undergoes increased erythropoiesis to compensate for excessive hemolysis in an attempt to correct anemia. RBC production may increase by 8- to 10-fold to maintain normal hemoglobin levels. Thus, anemia may not become evident if bone marrow is able to compensate for increased RBC destruction. Compensated hemolytic state is termed when a person has increased reticulocyte count with erythroid hyperplasia in the bone marrow along with decreased RBC survival evident by (1) increased plasma lactate dehydrogenase (LDH) level (2) reduced plasma haptoglobins (3) studies revealing reduced red cell survival, etc. Hemolytic anemia is termed only when the compensatory mechanisms have failed and the individual develops anemia.

In certain conditions, the major defect is impairment of RBC production which plays a major role, e.g., leukemia, aplastic anemia, malignant lymphomas, liver or renal disorders, rheumatoid arthritis, myelodysplastic syndromes, megaloblastic anemias, etc. These conditions may be associated with reduced RBC survival but the clinical features of hemolytic anemia are absent. Sometimes hemolytic process may become evident with the increase in hemoglobin level after packed cell transfusion which is not well sustained. However, all these conditions are not considered as hemolytic anemia.

INTRACORPUSCULAR DEFECTS

Red blood cell has three main components, viz., (1) red cell membrane, (2) hemoglobin molecule and (3) various enzymes involved in red cell metabolism. Defects in any of three can result in hemolytic anemia (**Box 1**). These disorders are inherited congenital disorders which usually present in infancy and early childhood. However, some of the disorders may manifest even during adulthood.

EXTRACORPUSCULAR DEFECTS

These are important causes of hemolytic anemia in which RBCs are normal but their survival is reduced as result of problems in the plasma. These conditions are acquired and hemolysis results from immune or nonimmune mechanisms (**Box 2**). These disorders often present later except hemolytic disease of the newborn which often present in the first few days of life.

DIAGNOSIS OF HEMOLYTIC ANEMIA

Whenever any child is suspected to have hemolytic anemia, effort should be made to get the answer for following questions:

1. Is the anemia hemolytic?
2. Severity of anemia and whether the onset is acute or insidious?
3. Is RBC destruction due to intrinsic or extrinsic etiology?

Reduced survival of RBC is the hallmark of hemolytic anemia but the RBC survival studies for its diagnosis are not practical. Thus, the diagnosis of hemolytic anemia is determined by evidences of increased red cell destruction and increased hematopoietic regeneration. Generally clinical features to all hemolytic anemia

BOX 1 Intracorporeal defects/congenital hemolytic anemia

RBC membrane defects

- Hereditary spherocytosis (HS)
- Hereditary elliptocytosis (HE)
- Hereditary stomatocytosis
- Acanthocytosis (*abetalipoproteinemia*)

Hemoglobin (Hb) defects

- Sickle cell anemia
 - Unstable Hb disease, HbC, HbD, HbE
- *Thalassemia*: α - or β -thalassemia
- Sickle cell β -thalassemia, HbE β -thalassemia, HbD β -thalassemia, etc.
 - Double heterozygous disorders

Enzyme defects

- Glucose-6-phosphate dehydrogenase deficiency
 - Glutathione reductase/synthetase
 - Adenylate kinase deficiency
- Pyruvate kinase deficiency
 - Hexokinase
 - Glucose phosphate isomerase
 - Phosphoglycerate kinase
- Drug-induced hemolytic anemia
- Favism

BOX 2 Extracorporeal defects/acquired hemolytic anemia

Immune causes

- Autoimmune hemolytic anemia
 - Warm antibody
 - Cold antibody
- Incompatible blood transfusion
- Drug induced

Nonimmune

- Paroxysmal nocturnal hemoglobinuria
- Cardiac hemolytic anemia
- Microangiopathic hemolytic anemia
- March hemoglobinuria

Secondary

- Bacterial (cholera, *Salmonella*, clostridial, Gram positive infections, etc.)
- Protozoa (malaria, toxoplasmosis, leishmaniasis)
- Burns
- Lead poisoning
- Thermal injury
- Snake venoms

are common but presence of some features along with evidences for intravascular or extravascular causes for hemolysis are helpful in determining the etiology of anemia.

Intravascular hemolysis is an acute process where RBC destruction releases free hemoglobin which binds with haptoglobin resulting in low haptoglobin levels. Extravascular hemolysis results from increased removal of senescent RBC by process of phagocytosis by the reticuloendothelial system. Hemoglobin released is catabolized by phagocytic cells and thus there is no increase of free hemoglobin in plasma though the serum bilirubin levels are raised in some condition.

Evidence of Hemoglobin Breakdown

Jaundice and hyperbilirubinemia Increase in unconjugated bilirubin and presence of jaundice are often present in several hemolytic disorders. Unconjugated serum bilirubin varies between 3 mg/dL and 5 mg/dL and is evident on the sclera. However, its levels may be high in hemolytic crisis, hemolytic disease of the newborn, hemoglobin E disease, development of hepatitis (A or E) in presence of glucose-6-phosphate dehydrogenase (G6PD) deficiency, etc.

The bilirubin levels depend upon combination of multiple factors, viz., amount and rate of RBC breakdown and the ability of liver to conjugate or excrete the bilirubin. Thus, the serum bilirubin level does not correlate with rate of hemolysis. Jaundice is often present but its absence does not exclude the hemolytic state or anemia if the liver is able to conjugate and excrete the excess of bilirubin efficiently. Hemolytic jaundice is predominantly unconjugated which does not appear in the urine and it does not cause pruritus. However, in presence of complications such as gallstones, liver disease (cirrhosis), conjugated bilirubin levels may be increased.

Plasma haptoglobin Haptoglobins are α_2 -glycoproteins which combine with hemoglobin and its products. They are synthesized in the liver. Hemoglobin molecule is very small when it binds with haptoglobin and its derivatives to form a larger complex which is rapidly removed by the parenchymal cells of the liver. In hemolytic states, there is increased release of hemoglobin and thus the plasma haptoglobin levels get reduced in hemolytic anemia which return to normal levels with 4–6 days. However, in chronic hemolytic condition, its levels continue to remain low.

Plasma hemopexin Hemopexin is a β -glycoprotein and it binds with free heme molecule. In severe hemolytic condition when large amount of hemoglobin is released and haptoglobin gets fully saturated then unbound hemoglobin is converted to methemoglobin. Subsequently methemoglobin breaks into ferriheme and globin. Ferriheme combines with hemopexin to form a complex which is cleared by liver in similar way as haptoglobin. Hemopexin levels are low as it gets utilized in forming a complex with ferriheme in intravascular hemolytic conditions.

Lactate dehydrogenase Plasma levels of LDH are increased in hemolytic anemia and megaloblastic anemia because of ineffective erythropoiesis. LDH levels are also raised in other disorders such as myocardial or pulmonary infarction, muscle diseases, lymphoma, leukemia, etc. Thus, it is not diagnostic only for hemolytic states.

Evidence for Intravascular Hemolysis

Hemoglobinuria and hemosiderinuria Hemoglobin from destroyed RBC is released in the plasma during intravascular hemolysis. If the released hemoglobin levels exceed, the haptoglobin binding capacity in such situations unbound hemoglobin passes through the glomerular membrane which is reabsorbed in the proximal renal tubules. However, if the proximal tubules are unable to absorb because of its excessive load, it appears in the urine as hemoglobinuria. The urine color may vary from pink to black. Hemoglobinuria can be easily distinguished from hematuria by urine microscopic examination. In the renal tubular cells, globin is degraded and heme iron is stored in the tubular cells. Gradual loss of iron-laden tubular cells appears as hemosiderin in the urine. Hemosiderin can be demonstrated in the centrifuged urine sediment by Prussian blue stain as extracellular or intracellular granules. It is often present in chronic hemolytic anemia such as paroxysmal nocturnal hemoglobinuria (PNH).

Urobilinogen The bilirubin breakdown major product is urobilinogen which is mainly excreted through feces and small amounts in the urine. Usually urobilinogen is not measured as it is not practical and the difficulties in its technique and interpretation.

Red Blood Cell Changes

Several hemolytic anemias are characterized by changes in RBC. Presence of spherocytes, sickle cells, red cells fragmentation, Heinz body, increased osmotic fragility (OF) whenever present strongly suggests the presence of hemolytic anemia. Thus, detailed examination of peripheral blood film by an expert is of utmost importance and often provides clue for the underlying condition.

Spherocytes RBCs which are more spheroidal with decreased diameter are termed as spherocytes. Spherocytes have reduced

surface area while their volume may be normal or slightly reduced. These cells appear as small, round, deeply staining cells with hardly any central pallor. Spherocytes are seen in hereditary spherocytosis in which there is intrinsic defect in red cell membrane. Among the acquired conditions such as autoimmune hemolytic anemia, hemolytic disease of the newborn, burns, thermal injury, etc., the spherocytes are present in varying number. Thus, their presence is not diagnostic of underlying etiology. Spherocytes vary between 15% and 20% are present in HS and autoimmune hemolytic anemias while in other disorders the spherocytes are usually around 5%.

Osmotic fragility Spherocytes have increased lysis in hypotonic solution. Percentage of red cell lysis is measured in different concentration of saline solution. Normally 50% of red cell lysis occurs between 4.0 g/L and 4.5 g/L of sodium chloride. Increased OF occurs in presence of spherocytes. OF gets accentuated by incubating RBC for 24 hours. Increased OF only confirms the presence of spherocytes or elliptocytes but is not diagnostic of underlying cause of hemolytic anemia on same lines as presence of spherocytes and elliptocytes.

Sickle cells Red cells acquire the sickle or elongated shape and these cells are present on peripheral blood. In sickle cell disease, the red cells become sickle shaped due to intracellular polymerization of HbS which is reversible upon reoxygenation. Sickling of red cells can be induced by sealing a drop of blood under a coverslip to exclude oxygen by adding 2% sodium metabisulfite. Reducing agent such as sodium dithionite if added to hemolysate it forms deoxy-Hbs complex which is insoluble and renders the solution turbid. The test is termed as solubility test. Presence of sickle cells alone or in combination of positive sickling phenomenon or positive solubility test cannot distinguish sickle cell trait from sickle cell anemia. However, presence of sickle cells on blood smear/sickling phenomenon/positive solubility tests are diagnostic of inherited sickle cell disorder.

Red blood cell fragmentation Fragmented RBCs are irregularly contracted cells having different shapes and sizes appearing as crescent, triangular, comma shaped deeply staining cells. Presence of such cells in significant number is suggestive of hemolytic anemia. These cells are also seen in hemolytic anemia secondary to cardiac diseases, microangiopathic states, e.g., disseminated intravascular hemolysis, chemical hemolytic anemia, etc. Presence of RBC fragmentation is not diagnostic of any specific hemolytic disorder.

Heinz body These are aggregates of denatured globulin and can be demonstrated in RBC by supravital staining. However, significant number of Heinz bodies may be present in various hemolytic anemias such as thalassemia syndromes, hemoglobin H, exposure to oxidant drugs and chemicals and following splenectomy.

Target cells Red cells with hemoglobin in the center with pallor around and peripheral hemoglobinized red cells are termed as target cells. Thus, cells are present in good number in thalassemia, homozygous hemoglobinopathies, following splenectomy and in obstructive jaundice. Presence of these cells supports the diagnosis of hemolytic anemia but further tests are essential to determine the underlying etiology.

Evidence of Erythroid Hyperplasia

Hemolytic anemia results in increase in erythropoietin level in response to chronic hypoxia. Erythropoietin stimulates the erythropoiesis in the bone marrow resulting in reticulocytosis, polychromatic macrocytes in blood and erythroid hyperplasia in the marrow (**Box 3**). Absolute reticulocyte count is now readily available in five part cell counters which are reliable and accurate. Reticulocytosis does not occur proportional to the severity of anemia. However, it varies between 5% and 20%. Its levels are higher in disorders like autoimmune hemolytic anemia and HS as compared with other hemolytic anemias. It may be used as an

index of RBC production. It is desirable to determine corrected reticulocyte count which is proportional to the hematocrit or hemoglobin level. Additional benefit of automated cell counters is that it can identify stress reticulocytes based upon their increased volume and RNA content. Nucleated RBCs (normoblasts) are often present in blood, which are also proportional to the severity of anemia. However, normoblast number is high in hemolytic disease of the newborn and after splenectomy in patients with hemolytic anemia. Reticulocyte count is also high in response to hematinic therapy in nutritional anemia.

Polychromasia macrocytosis Chronic hypoxia results in high levels of erythropoietin production which in turn leads to premature release of reticulocytes, which are larger in size and appear as polychromatic cells. As these cells mature, the polychromasia disappears but the RBC continues to have large size (macrocytosis). Presence of these cells in blood results in higher number results in high mean cell volume (MCV) of RBC. Macrocytosis is more pronounced following acute episodes than chronic hemolytic disorders. However, macrocytosis does not occur in conditions like HS and sickle cell anemia. In addition, leukocytosis and thrombocytosis may be observed in some cases as a part of bone marrow hyperplasia.

Bone marrow hyperplasia Bone marrow aspirations appear more cellular and contain less fat. Bone marrow shows normoblastic erythroid hyperplasia with myeloid erythroid ratio may become 1:1 or less. Megaloblastoid changes may be present secondary to folic acid deficiency. Similarly bone biopsy is hypercellular and may show sheets of erythroid cells.

Bony changes Marrow hyperplasia in thalassemia often results in bony changes. Broadening of diploic spaces and thickening of frontal and parietal bones occur which are seen as *hair-on-end* appearance on X-ray of skull and these changes are more remarkable in frontal and parietal bones. On other hand, thinning of cortex along with widening of marrow cavity occurs in tubular bones of hand (carpal and metacarpals) along with decreased density of the medullary area which may appear as coarse and this has been termed as trabecular pattern. Similar changes may be present in ribs. The vertebral bodies become short and widened. These changes are more marked in thalassemia major while bony changes are mild and infrequent in HS, enzymopathies, etc.

History and Examination

Congenital hemolytic anemia Onset of anemia is usually mild to moderate. Children remain asymptomatic even for years except in cases with thalassemia major. Children with thalassemia intermedia, Hb E/ β -thalassemia often present late. Sometimes these cases present initially with complications of gallstones, growth, retardation or fractures of long bones, leg ulcers, etc. **Table 1** summarizes the difference in clinical features between congenital and acquired hemolytic anemia.

Age of onset Anemia presenting in newborn period has different causes (**Box 4**) as compared with hemolytic anemia presenting

later. Simple algorithm for anemia presenting in newborn is given in **Flow chart 1** which is helpful for diagnosis.

Acute onset Acute onset is often present in patients with acquired hemolytic anemia who present with malaise, weakness, backache, headache, breathlessness. History of black color urine is suggestive of intravascular hemolysis. Jaundice may be present and bilirubin level is usually up to 5 mg/dL.

Jaundice It is usually mild to moderate and is of unconjugated type. It is not associated with pruritus while jaundice in Rh or ABO incompatibility is very high and may cause kernicterus in neonate if not detected early and treated as an emergency. Patients with enzymopathy especially with G6PD present with high bilirubin either following drug exposure or infections. Jaundice in G6PD deficiency is mild but development of hepatitis in G6PD deficiency results in high serum bilirubin level. Splenomegaly is generally mild to moderate in nature and it may increase with advancing age. However, in patients with sickle cell anemia, spleen size decreases due to autoinfarction as the child grows. In patients of HS, splenomegaly may be the only clinical presentation and patients may have mild anemia. Leg ulcers, often present in sickle cell anemia, may also develop in patients with hereditary spherocytosis and non-transfusion-dependent thalassemia.

Table 1 Difference in clinical features of congenital and acquired hemolytic anemia

Features	Congenital	Acquired
Race	Common in certain races and regions	Uncommon
Inheritance	Usually inherited	Acquired
Family history	Positive	Negative
Age	Starts from infancy	Second decade
Onset	Insidious	Acute
Anemia	Mild to moderate	Severe
Jaundice	Mild, moderate or severe	Mild to moderate during acute episode Absent in insidious onset
Bony changes	Often present	Absent
Splenomegaly	Present	Usually absent
Leg ulcer	May occur in sickle cell anemia	Absent
Cholelithiasis	May occur in thalassemia, hereditary spherocytosis, and sickle cell anemia	Absent

BOX 4 Causes of neonatal hemolytic states

Immune hemolytic anemia

- ABO and Rh incompatibility

Nonimmune hemolytic anemia

- **Disorders of red cell membrane:** Hereditary spherocytosis, hereditary elliptocytosis, hereditary stomatocytosis
- **Red cell enzyme deficiencies:** Glucose-6-phosphate dehydrogenase deficiency, pyruvate kinase deficiency, etc.
- **Thalassemias:** α -thalassemia, β -thalassemia, compound double heterozygous
- **Hemoglobinopathies:** Sickle cell anemia
- **Infection/septicemia:** Gram positive and gram-negative, intrauterine infections (TORCH), malaria
- Disseminated intravascular coagulopathy
- Galactosemia
- Drug induced

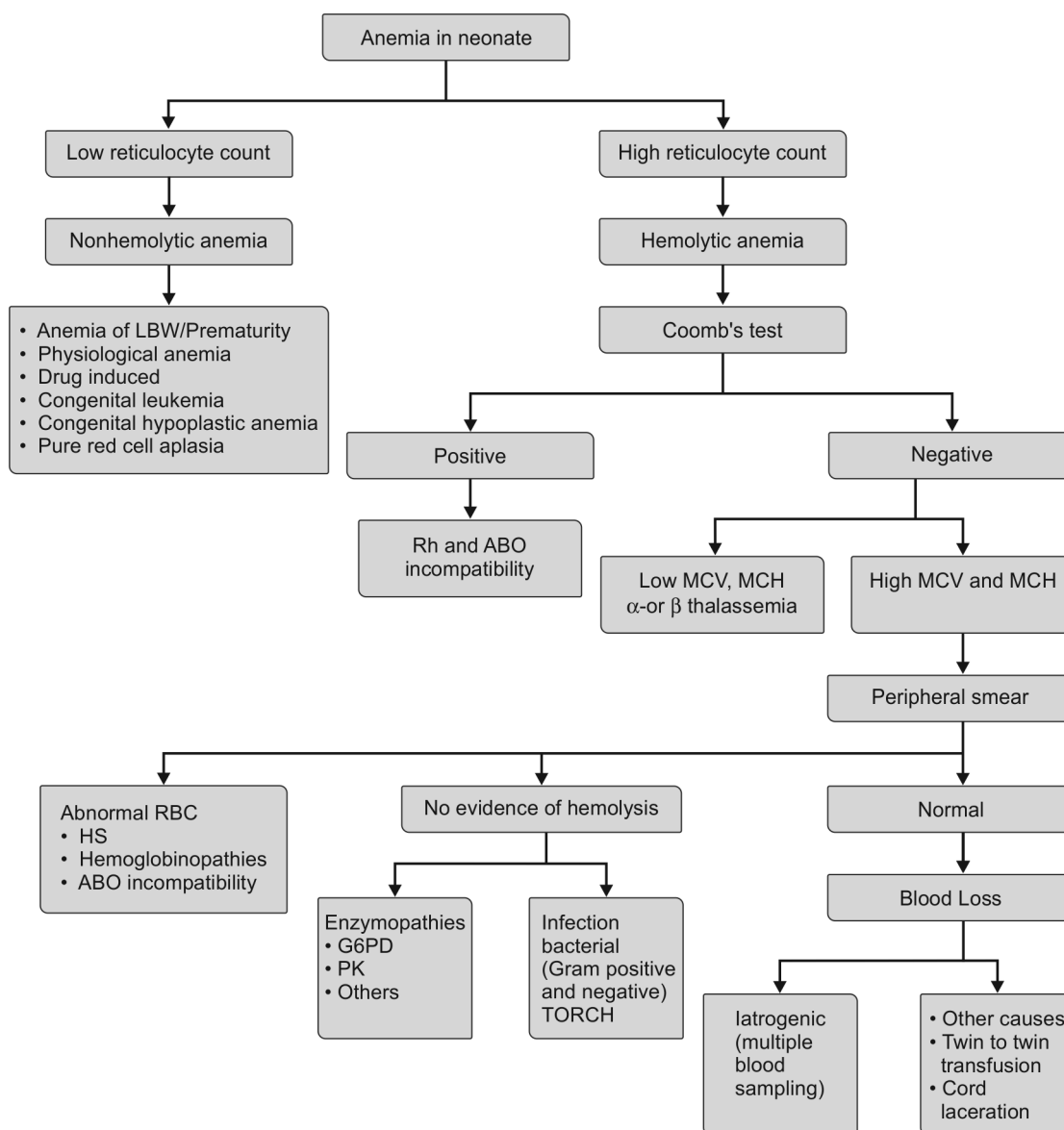
BOX 3 Laboratory evidence of erythroid hyperplasia

Blood

- Reticulocytosis (polychromasia, basophilic stippling), nucleated RBCs
- Macrocytosis
- Leukocytosis and thrombocytosis
- Ferrokinetic studies showing increased plasma iron turnover

Bone marrow

- Normoblastic erythroid hyperplasia
- Myeloid and erythroid ratio 1:1
- Bone biopsy showing hypercellularity with sheets of erythroid cells

Flow chart 1 Algorithm for approach to hemolytic anemia in neonate

Abbreviations: LBW, low birthweight; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; HS, hereditary spherocytosis; PK, pyruvate kinase deficiency; G6PD, glucose-6-phosphate dehydrogenase.

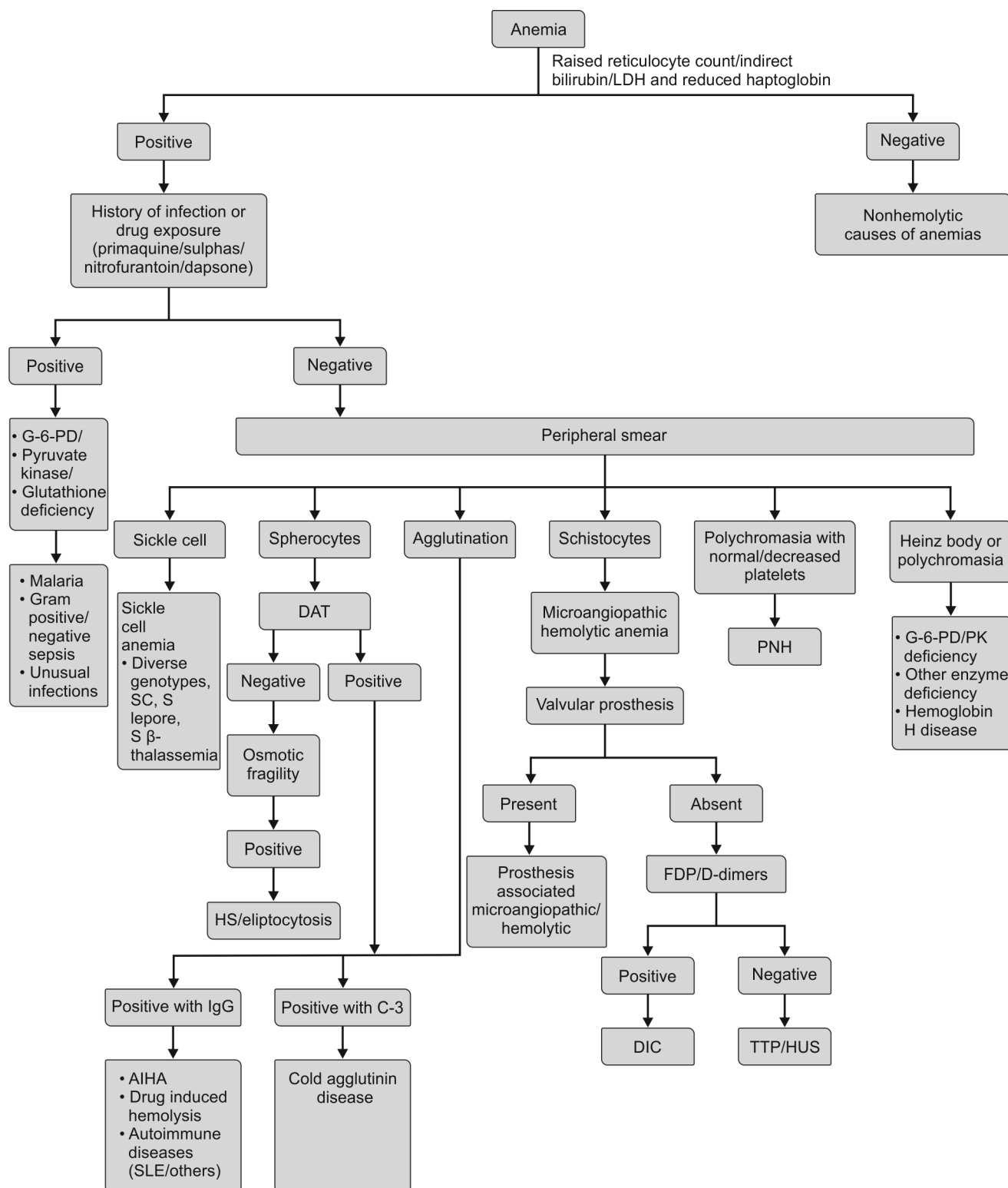
Cholelithiasis Many patients with hemolytic anemia (thalassemia, HS, sickle cell anemia, non-transfusion-dependent thalassemia (NTDT) may develop gallstones because of increased pigment load. The prevalence of cholelithiasis increases with advancing age. The children with cholelithiasis are at higher risk of developing cholecystitis and obstructive jaundice. These children at times may present as acute abdomen.

Features of underlying conditions Patients with lymphomas, immune disorders such as rheumatoid arthritis, systemic lupus erythematosus (SLE), antiphospholipid syndrome may develop acquired hemolytic anemia. These disorders are more common in adults than in children. Clinical manifestations of these disorders provide a clue for presence of hemolytic anemia and underlying etiology.

APPROACH TO A CHILD WITH HEMOLYTIC ANEMIA

Causes of hemolytic anemia are variable from inherited to acquired causes (**Boxes 1 and 2**). A detailed history of onset of symptoms (acute or insidious) along with duration of the illness,

family history of similar disease or history of blood transfusion to the patient and family members, course of the disease are helpful. The origin of the family, its race and region are also of great help as certain hemolytic anemias are widely prevalent in certain region, e.g., HbE in Northeastern states of India, Burma, and Thailand. There is a sickle cell belt across Madhya Pradesh, Maharashtra, Orissa in India while sickle cell anemia is very common in Africa. Inherited disorders often present from early childhood and are of insidious onset. On other hand, acquired causes of hemolytic anemia are generally of acute onset, present late and family history is usually negative (**Table 1**). Examination revealing the presence of anemia, jaundice, hemolytic facies, growth retardation, hepatosplenomegaly evidences of recurrent infection, dactylitis and chronic leg ulcers are helpful for diagnosis of hemolytic anemia. Detailed clinical presentation and diagnostic criteria of various hemolytic anemias are given in respective Chapters. General approach along with algorithms is included which guides the clinicians how to proceed to make a definitive diagnosis with minimal investigations (**Flow charts 1 and 2**).



Many hemolytic disorders are episodic in nature and thus all test may be negative in the absence of active hemolysis

Abbreviations: LDH, lactate dehydrogenase; G6PD, glucose-6-phosphate dehydrogenase; DAT, direct antiglobulin test; AIHA, autoimmune hemolytic anemia; SLE, systemic lupus erythematosus; DIC, disseminated intravascular coagulation; TTP, thrombotic thrombocytopenic purpura; HUS, hemolytic uremic syndrome; FDP, fibrin degradation products; PNH, paroxysmal nocturnal hemoglobinuria; PK, pyruvate kinase deficiency.

Investigations in Hemolytic Anemia

Detailed peripheral examination is of utmost importance which provides clue for various underlying causes. Presence of high reticulocyte count, unconjugated bilirubin, LDH levels and reduced haptoglobin levels are suggestive of hemolytic anemia. It is preferable that blood should be taken prior to blood transfusion for initial peripheral smear, special tests such as Heinz bodies, hemoglobin electrophoresis, osmotic fragility, G6PD and other enzymopathies as all these tests get altered following blood transfusion. List of test which is usually required to confirm the diagnosis is given in **Box 5**. Based upon the detailed history, examination along with

red cell morphology and reticulocyte counts, it is essential to have a clinical diagnosis and minimum number of test should be done to make a correct diagnosis so that appropriate treatment can be initiated.

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BOX 5 Investigations for hemolytic anemia

Essential tests

- Full blood examination, with special reference to: Morphology of RBCs—spherocytes, sickle cell, autoagglutination, fragmentation, inclusion bodies, etc. (**Flow chart 2**)
- Reticulocyte count
- Plasma haptoglobin level
- Serum bilirubin level (unconjugated)
- Osmotic fragility test
- Direct antiglobulin test
- Antibody screening
- Sickling test/solubility test
- Tests for abnormal hemoglobin: Hemoglobin electrophoresis, high-pressure liquid chromatography, HbH inclusions, etc.
- Examination of urine for urobilinogen, hemoglobin, hemosiderin

Special investigations

- RBC survival studies (for establishing hemolytic anemia in doubtful cases)
- Bone marrow aspiration and biopsy (evidence of erythroid hyperplasia, folate deficiency, lymphoma and other secondary causes)
- Plasma for hemoglobin and methemalbumin (for confirming intravascular hemolysis)
- X-ray of skull, hands and long bones
- Family studies for hereditary hemolytic anemias
- Heinz body preparation (hereditary hemolytic anemia, chemical hemolytic anemia)
- Enzyme studies G6PD, PK and other enzymes
- Cold agglutinins (AIHA)
- Tests for secondary AIHA - LE cell test, ANA, lymph node biopsy, etc.
- *Paroxysmal nocturnal hemoglobinuria test*: Ham's acid serum test, sucrose hemolysis test, CD55, CD59
- Donath-Landsteiner test for paroxysmal cold hemoglobinuria

IN A NUTSHELL

1. Whenever any child is suspected to have hemolytic anemia, effort should be ascertain if RBC destruction is due to intrinsic or extrinsic etiology?
2. *Hemolytic anemia is characterized by either or more of the following*: Hemoglobin breakdown, intravascular hemolysis, presence of spherocytes, fragmented red cells, and erythroid hyperplasia.
3. Evidence of hemoglobin breakdown includes jaundice and hyperbilirubinemia, increased plasma haptoglobin and hemopexin, and increased plasma LDH.
4. Evidence for intravascular hemolysis includes anemia, hemoglobinuria, and hemosiderinuria.
5. Red blood cell changes suggesting hemolysis includes presence of spherocytes, fragmented red cells, target cells, Heinz bodies, or increased OF.
6. Erythroid hyperplasia is suggested by reticulocytosis, presence of normoblasts and erythroid hyperplasia in bone marrow.

Chapter 38.9

Hemoglobinopathies

HP Pati, Deepti Mutreja

Hemoglobinopathies are defined as a group of genetic disorders caused by production of a structurally abnormal hemoglobin (Hb) molecule, where the amino acid sequence is altered and an unusual (variant Hb) is produced, e.g., hemoglobin S (HbS), hemoglobin E (HbE), hemoglobin C (HbC), hemoglobin D (HbD), etc. The quantitative disorders are the *thalassemia group of disorders*. Normal Hb constitution according to age is shown in **Table 1**.

EPIDEMIOLOGY

Hemoglobin E is found predominantly in Southeast Asia, India, China and Sri Lanka. A potentially large population; approximately 5–50% in Northeastern states of India are carriers of HbE. HbD Punjab (also known as HbD Los Angeles) occurs mostly in Northwest India, Pakistan and Iran. The greatest prevalence of HbD Punjab is among *Sikhs* in Punjab in India where it is reported to be around 2%. HbC has been described in United States among blacks where the prevalence is 2–3%. It has also been observed in Italians, Africans and Turkish populations.

STRUCTURAL HEMOGLOBINOPATHIES

This group of Hb disorders is caused by structural defects resulting from an altered amino acid sequence in α - or β -chains due to a point mutation. The mutation could result in either no physiological abnormality, i.e., clinically asymptomatic individuals HbQ India, O Indonesia, O Arab; variants with a tendency to aggregate, e.g., HbS and HbC; variants with abnormal Hb synthesis, e.g., HbE, HbD Punjab, HbD Iran; variants with a tendency to precipitate and with hemolysis (unstable Hbs), e.g., Hb Köln; variants with altered oxygen affinity, e.g., Hb Johnstown; variants with decreased oxygen carrying capacity (HbM); variants with fast moving in alkaline electrophoresis, HbJ group. Electrophoresis pattern of normal Hb is shown in **Figure 1**.

Table 1 Major hemoglobins (Hbs) and their constitution in normal adults, infants and intrauterine period

Hemoglobin	Globin chain composition	Remarks
HbA	$\alpha_2\beta_2$	Physiologically important Hb in normal adults; 95–96%
HbF	$\alpha_2\gamma_2$	Major physiologic Hb in postembryonal fetuses. Less than 1% in normal adults
HbA ₂	$\alpha_2\delta_2$	Slightly elevated in most β -thalassemias, but may be decreased in iron deficiency, thus making it an ingenious marker for evaluating microcytic, hypochromic anemias. Normal values are up to 3.5% in adults
Gower 1	zeta2epsilon2 ($\zeta_2\epsilon_2$)	Very early normal embryonal
Gower 2	$\alpha_2\epsilon_2$	Hbs that disappear after 8 weeks of gestation. The only one of clinical importance is Hb Portland, which may be seen at birth in cases of the severe form of α -thalassemia
Portland	zeta2gamma2 ($\zeta_2\gamma_2$)	

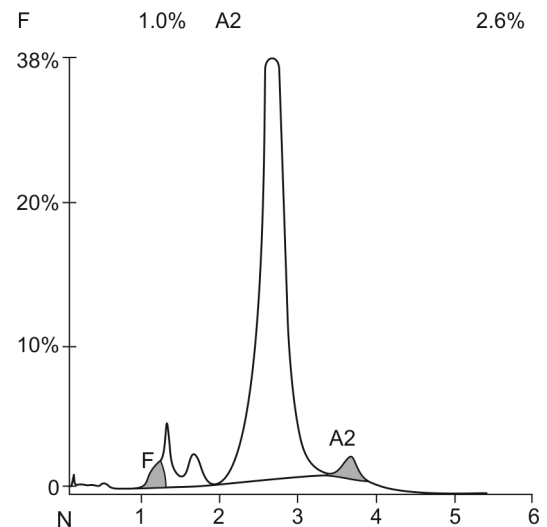


Figure 1 Normal hemoglobin high-performance liquid chromatography (HPLC)

Hemoglobin C Disease

Hemoglobin C is produced when lysine is substituted for glutamic acid at the sixth position in the β -chain ($\beta^{6\text{glu}\rightarrow\text{lys}}$). Intraerythrocytic crystals of oxygenated HbC can be found and this crystal formation is enhanced when cells are dehydrated or in hypertonic solution. These erythrocytes become rigid and are trapped and destroyed in the spleen.

Hemoglobin C homozygosity, or HbC disease, progresses in a similar way to sickle cell disease, but is less severe. Variable hemolytic anemia is the most dominant form. Clinically mild to moderate splenomegaly is common. Laboratory evaluation shows Hb in the range of 10–11 g/dL. Blood film shows an abundance of target cells, occasional microspherocytes, and HbC crystals especially in splenectomized patients. Hb analysis shows more than 90% HbC with slight increase in HbF. On cellulose acetate electrophoresis at alkaline pH, HbC migrates with HbA₂, HbE and HbO Arab. HbC can be separated from these other HbS by citrate agar electrophoresis at acid pH. HbC trait is asymptomatic. The coinheritance of HbC with HbS and β -thalassemias results in a wide spectrum of hemoglobinopathies with varying degrees of severity.

Hemoglobin E Disease

Hemoglobin E is the second most prevalent hemoglobinopathy worldwide. HbE is a result of the substitution of lysine for glutamic acid in the β -chain at the 26th amino acid ($\beta^{26\text{glu}\rightarrow\text{lys}}$). The β^E -allele is mildly thalassemic due to the activation of a cryptic splice site, and when it is inherited together with β^0 -thalassemia, there is a marked deficiency of β -chain production.

Homozygous HbE is characterized by the presence of a mild asymptomatic microcytic hypochromic anemia. Target cells are prominent. Hb analysis reveals 90% or more HbE with the remainder HbF and HbA₂. On alkaline electrophoresis, HbE migrates with HbA₂, HbC and HbO Arab. On agar gel at acid pH, HbE migrates with HbA. HbE trait is asymptomatic with 35–45% HbE on Hb analysis.

Compound heterozygosity for HbE/ β -thalassemia causes a moderate to severe anemia similar to thalassemia. The diagnosis is confirmed by finding only HbE and HbF on Hb analysis (**Fig. 2**) and by demonstrating HbE trait in one parent and β -thalassemia trait in the other. In other cases of HbE/ β^+ -thalassemia, variable quantities of HbA are present and the condition is milder. Hb EE state is clinically associated with mild anemia like β -thalassemia trait.

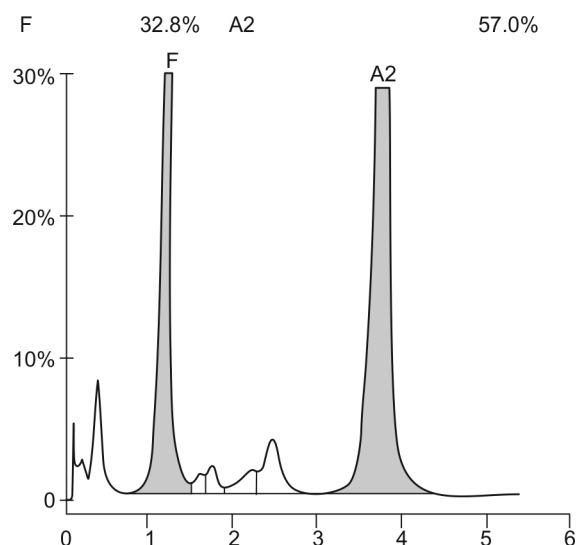


Figure 2 Hemoglobin HPLC in HbE β -thalassemia showing prominent peaks of HbF and HbE (eluting with HbA₂)

Hemoglobin D Disease

Hemoglobin D is the third variant Hb identified. The substitution in HbD is a glutamic acid to glutamine at the 121st amino acid of the β -globin chain ($\beta^{121}\text{Glu}\rightarrow\text{Gln}$). HbD migrates with HbS on alkaline electrophoresis. HbD heterozygotes are asymptomatic, nonanemic, and have normal red cell indices. Homozygotes for HbD-Los Angeles are asymptomatic and are hematologically normal with normal red cell indices. Blood films may show target cells. Osmotic fragility may be decreased. Compound heterozygotes for HbD-Los Angeles and a β^0 -thalassaemia mutation have mild microcytic anemia and show minimal hemolysis. Coinheritance of HbD-Los Angeles with HbS results in a severe sickle cell disease phenotype not different from homozygous HbS.

UNSTABLE HEMOGLOBIN DISORDERS

The unstable Hb disorders are a rare group of inherited hemolytic anemias that result from structural changes in the Hb molecule, which cause its intracellular precipitation with the formation of Heinz bodies. Prototypes include Hb Köln and Hb Zurich.

Molecular Pathology and Pathogenesis

Mechanisms that contribute to the instability of these mutant Hbs include mutations that weaken or modify the hemoglobin interactions, that interfere with the secondary or tertiary structure of the subunits, or that interfere with subunit interactions. As the unstable Hbs precipitate in the red cells or their precursors, they produce intracellular inclusions (Heinz bodies) which, together with oxidant damage to their membranes, make the cells more rigid and hence cause their premature destruction in the microcirculation.

Clinical Features

Patients with unstable Hbs can present in a number of ways, viz., congenital nonspherocytic hemolytic anemia with splenomegaly and pigmented (bilirubin) gallstones; Heinz body hemolytic anemia with sensitivity to oxidant drugs, such as sulfonamides; mild or minimal anemia with reticulocytosis out of proportion to the level of circulating Hb; thalassemia-like peripheral blood picture with hypochromic red blood cells; and increased formation of methemoglobin.

Laboratory Diagnosis

The diagnosis of an unstable Hb variant is established by the detection of Heinz bodies in red cells, the demonstration of Hb instability in the red cell hemolysate, and the presence of pigmenturia.

Management

Management of patients with an unstable Hb variant is mainly supportive, including the use of folic acid supplementation, transfusion when required, and in occasional patients, splenectomy.

CONGENITAL METHEMOGLOBINEMIA

In these cases, the amino acid substitution is near the heme pocket, close to iron molecule. The mutant Hb loses its ability to keep iron in the ferrous state and the resultant ferric iron is unable to carry oxygen. Several α - and β -globin variants associated with methemoglobinemia have been discovered. These disorders, unlike the genetic methemoglobinemias due to enzyme defects, follow a dominant pattern of inheritance. The patients are diagnosed by a history of cyanosis since birth, and may have mild polycythemia. Diagnosis is based on measuring methemoglobin levels by spectrophotometry, and analysis of Hb and DNA. No specific management is needed.

HIGH OXYGEN AFFINITY HEMOGLOBIN VARIANTS

Some Hb variants cause increased oxygen affinity, which results in varying degrees of polycythemia, e.g., Hb Bethesda. High oxygen affinity Hb variants result from amino acid substitutions at the interface of α - and β -subunits resulting in a molecule that are involved in the configurational changes which underlie heme-heme interaction or in others involve the amino acids concerned with the binding of 2, 3-DPG to Hb. This results in tight binding of oxygen to Hb resulting in functional anemia, with tissue hypoxia, which in turn causes an increased output of erythropoietin and an elevated red cell mass. The condition should be suspected in any patient with a pure red cell polycythemia associated with a left-shifted oxygen dissociation curve. The diagnosis can be confirmed by Hb analysis using chromatography, mass spectrometry or DNA analysis. In asymptomatic persons, no treatment is necessary. The difficulty arises if there is associated vascular disease, particularly coronary or cerebral artery insufficiency. As these patients require a high Hb level for oxygen transport, venesection should be carried out with great caution. Phlebotomy is undertaken to prevent high viscosity syndromes and typically the aim is to keep the hematocrit below 55%.

LOW-OXYGEN AFFINITY HEMOGLOBIN VARIANTS

This condition should be thought of in any patient with unexplained congenital cyanosis. The amino acid substitution in this variant was at the interface between α - and β -globin chains, giving rise to variants with a relatively low-oxygen affinity, e.g., Hb Kansas. Diagnosis is made by right-shifted oxygen dissociated curve. Hb levels and red cell mass are normal. No specific management is required as cyanosis is well tolerated if there is no physical exertion.

INVESTIGATIONS

Peripheral Blood Smear

In HbC disease, blood smear shows fully hemoglobinized RBCs confusing with sickled cells. In Hb EE disease, there may be plenty of target cells and mild hypochromia. In HbE β -thalassemia double heterozygous state, many bizarrely shaped, fragmented,

microcytic red cells and immature erythroid cells are seen as in cases of thalassemia major. Polychromasia and punctate basophils are also seen.

Biochemical Parameters

Serum bilirubin may be raised, serum haptoglobin and hemopexin are reduced. Serum ferritin, serum iron and iron binding capacity should be evaluated to distinguish from iron deficiency as mild anemia is common in many structural hemoglobinopathy. Also, many hemoglobinopathies are completely asymptomatic and there may be associated β -thalassemia trait or iron deficiency anemia to explain the anemia in them. Recommended assessment in hemoglobinopathy is shown in **Table 2**.

Hemoglobin Analysis

Cation-exchange high-performance liquid chromatography (CE-HPLC) or reverse phase HPLC Quantitative measurement of HbA₂, HbA and HbF allows the initial diagnosis of β -thalassemia trait as well as other β -thalassemia syndromes.

Hemoglobin Electrophoresis

Cellulose acetate in alkaline pH (pH 8.6) This simple method provides separation of the normal Hbs, HbA, HbF, and HbA₂ as well as the common variants HbS and HbC. On a cellulose acetate strip, HbA migrates the most towards the anode followed by HbF, HbS, and HbC.

Citrate agar in acid pH HbF, HbA, HbS, and HbC have distinct mobility patterns on citrate agar, which are different from those on cellulose acetate. The successive application of cellulose acetate and citrate agar electrophoresis allows for the definitive identification of HbS, HbC, HbE, and HbO Arab.

Isoelectric focusing Isoelectric focusing (IEF) on agarose gel is a good method for neonatal screening for hemoglobinopathies as it is sensitive to detect small amounts (less than 2%) of HbH.

Molecular Diagnostic Methods

Molecular diagnosis can be achieved by sequencing of the polymerase chain reaction (PCR) amplified globin gene PCR-based techniques including Gap PCR and reverse dot-blot hybridization techniques. Microarray-based detection methods for the identification of β -globin mutations can be used.

Multiple Ligand Probe Assay (MLPA) Gene amplifications, deletions, mutations and methylations of α - and β -genes have been identified by the MLPA technique.

IN A NUTSHELL

1. The term *hemoglobinopathy* includes all genetic Hb disorders.
2. The main types of abnormal Hb are HbS, HbE, and HbD and HbC. Within these main types there are several subtypes, with differing disease patterns.
3. Hemoglobin E in association with β -thalassemia can present with very variable clinical presentation from mild anemia to severe transfusion-dependent anemia.
4. Hemoglobin C is not seen in Indian subcontinent.
5. Awareness of hemoglobinopathies by education and counseling of families at risk is important for avoiding the burden of these to the society.

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Table 2 Recommended assessments in a child with hemoglobinopathy

	When	From age
<i>Initial diagnosis and counseling</i>		
Complete blood count, ferritin, transferrin saturation, hemolysis parameters, Hb testing, DNA testing if needed, blood groups, family appraisal, information on the disease, genetic counseling	On diagnosis	
• Complete blood count	Before and after each transfusion	
• Antibody detection test	Every 2 months	1 year onwards
• Serology: Hepatitis B/C, HIV, CMV	Annual status assessment	1 year onwards
<i>Iron metabolism</i>		
• Ferritin, transferrin saturation	At every transfusion	1 year onwards
<i>Liver function, liver iron</i>		
• ALT, AST, and GGT, bilirubin (total/direct)	Annual status assessment	1 year onwards
• Liver iron (MRI/biopsy)	Biannual status assessment	10 years onwards
<i>Cardiology</i>		
• Echocardiography	Annual status assessment	1 year onwards
• ECG		1 year onwards
• Cardiac MRI (if possible), chest X-ray		Adulthood
<i>Endocrinology</i>		
• Percentile growth curve	Every transfusion	1 year onwards
• Puberty stages, bone age/mineralization, testosterone/estradiol, LH, FSH, prolactin, cortisol, oral glucose tolerance test, thyroid parameters	Annual status assessment	10 years onwards 13–15 years onwards 10 years onwards 10 years onwards
• Serum calcium, phosphate	Monthly	10 years onwards

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Chapter 38.10 Thalassemia

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Thalassemia is group of inherited disorders of globin chain which were initially reported in 1920. Since this disorder was widely prevalent in Mediterranean region and was thus known as Mediterranean anemia. The word thalassemia was derived from Greek root "the sea" and "blood". However, presently it is prevalent all over the world and is the most common genetic disorder as per World Health Organization. It is inherited in a Mendelian recessive fashion. These disorders have been characterized at molecular level which has greatly helped in the understanding of its clinical presentation, course of the disease, and control of the disorder. However, these disorders are major public health problems in this millennium.

EPIDEMIOLOGY

Thalassemias occur at higher frequency from Mediterranean region through the Middle East and Southeast Asia. Nearly 4% of World's population is carrier of α - and β -thalassemia. In Southeast Asia 40 million are carriers. First case of thalassemia was published by Dr. Mukherjee from Calcutta in 1938. The mean prevalence of thalassemia is nearly 3.5% (1–17%). Its incidence varies in different regions and ethnic groups. Its prevalence is higher in communities like *Sindhis*, *Punjabis*, *Khatris*, *Gujratis*, *Mahars*, *Lohanas* and in certain *Muslim* and *Christian* communities. In India over 50 million persons are carriers of thalassemia. It is estimated that over 100,000 β -thalassemia major children are born all over the World and off these nearly 12,000 babies with β -thalassemia major are born only in India. There are evidences that milder form of β -thalassemia and carriers of β -thalassemia are protective against *Plasmodium falciparum* malaria.

MOLECULAR PATHOLOGY

Thalassemias were one of the first disorders which were characterized at the molecular level. These are caused by defects in synthesis of globin chain as a result of mutation in the globin gene. β -globin gene cluster is located on chromosome 11p15.5 while α -globin gene cluster is on chromosome 16p13.3 for alpha (α) (Fig. 1). In humans there are eight genetic loci which code for 6 types of globin chains. The genes on both globin cluster are

arranged 5'→3' on coding strands. β -globin chains is 60 kb long on which are located five functional genes 5'- ϵ - γ - δ - β -3'. The β -locus control region (LCR- β) between 5' and the ϵ -globin gene. Normal adult hemoglobin (HbA) is comprised of nearly 90–95% of total and minor component HbA₂ accounts for 2–3%. During fetal life and first few months of life fetal hemoglobin (HbF) is the main hemoglobin and it is present only in traces (<1%) in normal adults. Two most common types of thalassemia (α and β) result from decreased synthesis of α - and β -chains. Uncommon forms in which α - and β -chains or ϵ 1, gamma chain synthesis is defective resulting in $\delta\beta$ or $\epsilon\gamma\delta\beta$ thalassemias.

α -Thalassemia

Each individual inherits two α genes from each parent and thus genotype is written as $\alpha\alpha/\alpha\alpha$. α -thalassemia results from deletion of α gene or from a mutation that inactivates one of the pair. The homozygous state is written as $---/---$ and the heterozygous state as $---/\alpha\alpha$. On the other hand in α^+ thalassemia in which only one of α gene is lost. Then the homozygous and heterozygous states are termed as $-\alpha/\alpha\alpha$ and $-\alpha/-\alpha$ respectively. Clinical classification of α -thalassemia along with clinical presentation is given in Table 1.

β -Thalassemia

In this region β -thalassemia is most common which results from mutation in β -globin gene located on chromosome 11p15.5 (Fig. 1). This gene is constituted by three exons with two intervening sequences, 5' and 3' untranslated region (UTR) which is regulated by 5' promoter. β -locus control region (β -LCR) is another regulatory element of *HbB* gene located on upstream of promoter gene. Over 500 mutations have been reported all over the world and among these 5–10 mutations account for most cases in different region. These mutations can affect at any level such as transcription, processing of primary messenger, ribonucleic acid transcript, translation or post translational stability, etc. Rarely, β -thalassemia may also result from partial or complete deletion of β -globin gene. Some mutations result in complete absence of β -chain production and then the disorder is termed as β^0 thalassemia. When mutations result in reduced production of β -chain, then the disorder is called β^+ thalassemia. Individuals with β^0 mutations produce nonfunctional β -globin protein while others with β^+ produce reduced quantity of β -globin protein. Heterozygotes for β -thalassemia have mild anemia and raised HbA₂ levels and such individuals are termed as thalassemia minor/thalassemia carrier or thalassemia trait. In India five to eight mutations account for nearly 95% of cases with β -thalassemia major in different regions. These mutations are IVS-1-5(G→C), IVS-1-1(G→T) codons 8/9 (+G), codons 41/42 (-CTTT), 619 bp deletion, codon 15(G→A)-88 b (C→T), frameshift mutation codons 8/9 (+G). Mutations in (β -LCR) regions are uncommon.

All thalassemias result in imbalanced globin chain production. In β -thalassemia there is excess of α -chains which gets precipitated in precursor red cells causing reduced red cell survival in the bone marrow as well as in blood. While in α -thalassemia it is excess of γ -chains (Hbs Bart's) are produced forming γ_4 molecules in fetal and early life and H (β_4) molecules during childhood. These molecules are unstable and do not release the O₂ to the tissues because of high affinity of these molecules to oxygen leading to reduced oxygen delivery to various tissues.

PATHOPHYSIOLOGY

Excess of alpha chains precipitate to form inclusions in erythroid precursor leading to destruction of erythrocyte precursor cells in bone marrow leading to ineffective erythropoiesis and reduced red cell survival (Flow chart 1). Hemolysis is also contributed secondary to oxidization of α chains inclusions which cause

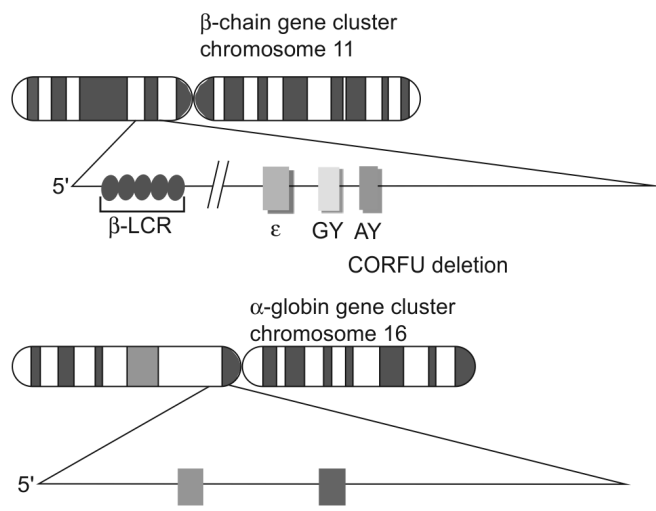
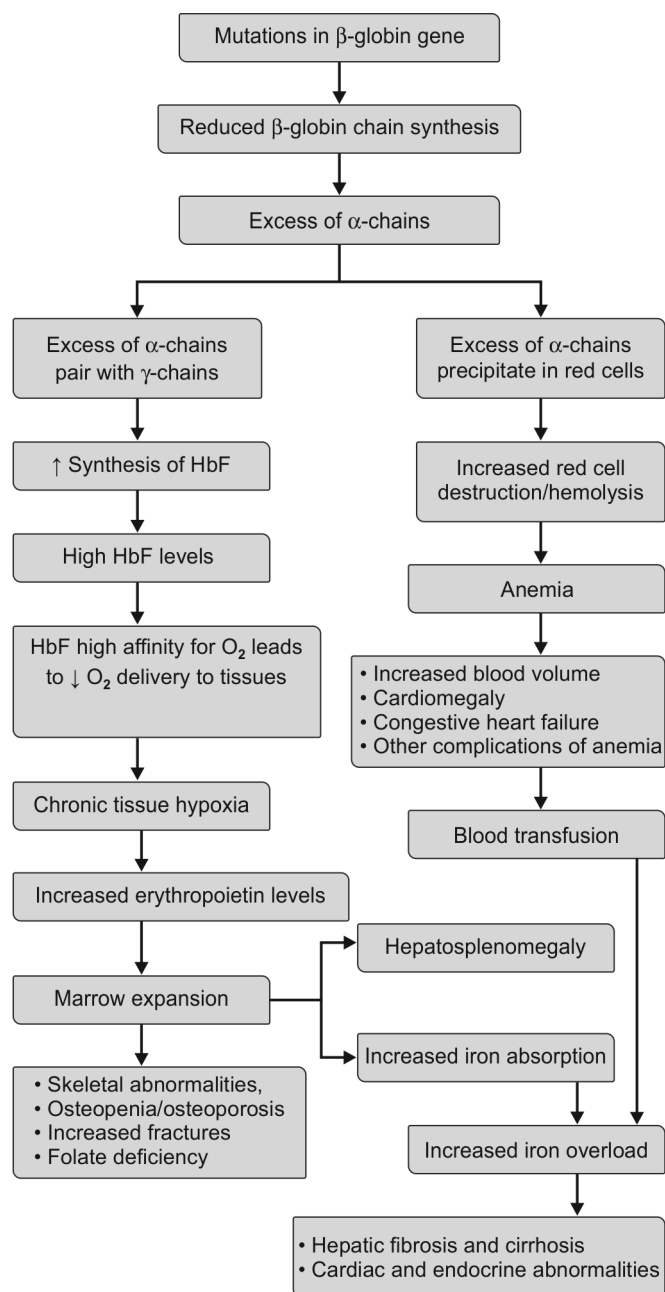


Figure 1 β - and α -globin gene cluster

Table 1 Classification of α thalassemia

Syndrome	Number of globin gene affected	Clinical picture	Hemoglobin pattern	Diagnosis
Silent carrier	One	Asymptomatic No anemia Normal red cells	1–2% Hb Bart (r_{μ})	Identification of mutations
α -thalassemia trait	Two	Mild anemia Microcytic hypochromic red cells	5–10% Hb Bart (r_{μ}) at birth low MCV and MCH	Identification of mutations
HbH disease	Three	Significant anemia hypochromic and microcytic picture hepatosplenomegaly	5–30% HbH (B_{μ})	Identification of mutations
Hydrops fetalis	Four	Severe anemia in fetal life. Hepatosplenomegaly, death in utero because of anemia	Mainly Hb Bart's, small amount of HbH	Identification of mutations

Flow chart 1 β -thalassemia pathophysiology

damage to red cell membrane. Molecular studies have revealed that excess of chains in β -thalassemia trigger the regulation of Fas and Fas ligand which play a major role in apoptosis of red blood cells and ineffective erythropoiesis with microcytic and hypochromic red cell morphology.

In response to anemia body secretes more of erythropoietin (EPO). Patients with high HbF levels have higher levels of EPO. High levels of EPO results in increase in erythropoiesis by 10–30 folds resulting in increase in metabolic activity, nutritional depletion of folic acid, growth stunting, increased cardiac load, congestive heart failure, etc. Splenomegaly primarily occurs secondary to increased entrapment of blood and to some extent due to extramedullary hematopoiesis. Large spleens may become hyperactive thus leading to exacerbation of anemia, increased blood requirements, thrombocytopenia and leukopenia. Such a state is termed as hypersplenism.

Iron overload in these children develops secondary to two main factors, viz. (a) increased iron absorption from gut secondary to excessive erythropoiesis and (b) transfusional iron which plays an important role. Normally iron is bound to plasma (transferrin) and storage proteins and there is hardly any level in form of toxic free radicals. In thalassemic patients transferrin and other iron binding proteins get saturated and free iron radicals cause widespread tissue damage through production of hydrogen peroxide (H_2O_2) and hydroxyl ions affecting liver, heart and endocrine organs. Iron in the liver is deposited in parenchymal and reticuloendothelial cells of liver leading to development of progressive liver fibrosis, cirrhosis and eventually carcinoma of liver.

Iron overload in the heart causes extensive myocardial fiber disruption and variable fibrosis which increases the uptake of toxic nontransferrin bound iron (NTBI) causing further cardiac damage. Free hydroxyl radicals cause damage to the lysosomal, membrane of myocytes further affecting cardiac functions adversely. Iron deposition in conducting system may lead to fatal arrhythmias.

Increase in erythropoietic activity results in marrow expansion resulting in body deformities, skeletal changes, and dental abnormalities. Other factors which contribute to bone pathology are secondary to endocrine disorders which include primary hypogonadism, growth hormone deficiency beside low vitamin D level, calcitonin levels and iron chelation therapy. These patients are prone to develop osteopenia, osteoporosis and bony fractures.

GENOTYPE AND PHENOTYPE CORRELATION

Thalassemia syndrome has a variable presentation from asymptomatic state to severe form requiring repeated blood transfusion within 6 month of age. Clinical presentation depends primarily upon the interaction among the following three genetic modifiers.

Primary Modifiers

Patients with β^0 homozygous mutations will hardly have β -chains and thus the disease will have severe form than baby having β^0 and β^+ mutations. In contrast child with β^+/β^+ with silent β thalassemia allele will have milder disease and present with mild to moderate anemia during late childhood. Some β -thalassemia allele will results in severe disease even in heterozygous state and have been termed as dominant β -thalassemia mutations. Nearly 30 alleles have been identified which are located in 3' third of exon 2 resulting in high levels of unstable β -globin protein which precipitate with β -globin chains. While some mutations are clustered in the promoter region are associated with high levels of HbF. The interaction of these factors affects the clinical presentation.

Secondary Modifiers

α -thalassemia α -thalassemia is also highly prevalent along with β -thalassemia in many regions of the world. Thus homozygous or compound heterozygous β -thalassemia patients who coinheritor α -thalassemia will have amelioration of clinical phenotype due to low levels of α -chains thus reducing the imbalance between α - and non- α -chains. Patients with single or double chain deletion will have milder clinical phenotype while patients with triple chain deletion will have clinical picture of thalassemia intermedia. In India, α 3.7 deletion is common among thalassemia intermedia cases.

α -Duplication/Quadruplication β -thalassemia carrier individuals who inherit excess of α -chains in form of triplicated or quadruplicated α -genes results in higher imbalance and thus these cases of thalassemia trait present as thalassemia intermedia. α -triplication has been observed in 5–20% of β -thalassemia intermedia in India.

Inherited disorders of hemoglobin These are group of autosomal recessive disorders of hemoglobin which are also common in some regions where thalassemia is common. Thus many people may inherit one of these along with thalassemia. Presence of these structural disorders has greater impact on the course of thalassemia. Among these hemoglobin E (HbE) and sickle cell disease (HbS) are common. These disorders are termed as compound heterozygosity.

HbE Beta globin variant G→A at codon 26 is known as HbE. HbE acts as a thalassemia variant associated with decreased beta globin production. The clinical phenotype of HbE beta-thalassemia is variable from very mild to severe transfusion dependent disease. In addition variation in phenotype occurs over the years with the decrease in transfusion requirement.

HbS It results from glutamic acid → valine amino acid substitution at 6th position of β -chain. Compound heterozygous state with β -thalassemia occurs frequently. Course of β -thalassemia in these cases is usually less severe and is variable depending upon the interaction of gene and whether it associated with β^0/β^+ inheritance.

Other hemoglobinopathies such as HbD Punjab and Hb-Q India are less common and have minimal impact on the natural course of thalassemia. On other hand HbD Iran is found among Iranian, Pakistanis, Jamaican Black and families in Northern Calabria, Italy. There is a mutation GAA → CAA at codon 22 of β chain responsible for HbD Iran. The prevalence of HbD Iran globin varies between 35% and 45%. It results in mild phenotype picture presenting as mild to moderate anemia with mild clinical pictures.

HbF levels It plays a major role as modifier of severity of β -thalassemia. Normally 5–8% of RBCs carry HbF and these cells are called F cells. Even small increase in HbF cells helps in ameliorating the severity of disease by reducing α versus non

α -globin imbalance. High levels of HbF occur in the following situations:

- β -thalassemia mutations in the promoter region are associated with high HbF levels.
- Increase in γ -chain synthesis results in prolonged red cell survival.
- Coinheritance of high of persistent fetal hemoglobin (*HPFH*) gene.
- Inheritance of Xmn 1-^s γ polymorphism was discovered initially which resulted in higher HbF levels in persons with homozygous β -thalassemia, E β or S β thalassemia. Association of this inheritance has resulted in delayed presentation with mild phenotype association.
- Single nucleotide polymorphisms (SNPs) in intron 2 of *BCL11A* gene on chromosome 2p16 is associated with raised HbF levels. Similarly, SNP presentation on three linkage disequilibrium block called HbSIL-MYB intergenic polymorphism (HMIP) block 1, 2 and 3 also results in high HbF levels.

Tertiary Modifiers

These modifiers neither affect the hemoglobin synthesis nor hemolysis but have adverse effect on the natural course of thalassemia. Patients with thalassemia have higher prevalence of jaundice and gall stones than general population as a result of excessive hemolysis. The risk of these complications gets enhanced in those with polymorphism in the promoter region of uridine diphosphate glucuronosyltransferase IA gene (*UGT1A*). Similarly, thalassemics having polymorphisms in vitamin D receptor gene and collagen type alpha genes are at much higher risk of developing osteopenia and osteoporosis.

Major Hemoglobin Disorders

Various hemoglobin disorders have been identified depending upon the mutations in α , β gene either alone or in combination with various inherited hemoglobin disorders (**Table 2**).

Table 2 Major hemoglobin disorders

<i>α-globin chain disorders</i>	<i>β-globin chain disorders</i>
HbH disease	• Thalassemia carrier
α -thalassemia (hydrops fetalis)	• Thalassemia intermedia (NTDT)
α -thalassemia	• Thalassemia major
	Compound thalassemia
	• HbS— β -thalassemia
	• HbE— β -thalassemia
	• HbD— β -thalassemia
	• Other rare thalassemia

CLINICAL PHENOTYPES OF β -THALASSEMIA

Clinical presentation is widely variable from asymptomatic state to severe anemia in the first few months of life. Based primarily upon the natural course of the disease, four types of phenotype presentations have been identified (**Table 3**).

Thalassemia Minor/Carrier/Trait

These individuals are usually asymptomatic or may have mild anemia. Anemia in some cases may worsen during stress like pregnancy, infection, etc. It is inherited as heterozygous β thalassemia. Hemoglobin levels may be normal or slightly reduced. Red cells have low mean corpuscular volume (MCV) less than 78 fL and mean corpuscular hemoglobin (MCH) less than 27 pg. Red blood cell counts are higher for the hemoglobin level. HbA₂ level is high more than 3.5% and is diagnostic. However, some β thalassemia mutations are so mild that even HbA₂ level in them

Table 3 Classification of β -thalassemia

Syndrome	β -globin gene affected	Clinical presentation	Hemoglobin pattern	Confirmatory diagnosis
Silent carrier	Heterozygous state	Asymptomatic persons without anemia	Normal with normal HPLC	Molecular studies
Thalassemia trait/carrier	Heterozygous state	Mild anemia \uparrow RBC count \downarrow MCV and MCH	HbA ₂ > 3.5%	Molecular studies
Thalassemia intermedia (NTDT)	Homozygous/heterozygous state	Moderate anemia not dependent on blood transfusion, hepatosplenomegaly Growth retardation, Bone abnormalities May require blood transfusion occasionally	Raised HbF or HbA ₂ level	Molecular studies
Thalassemia major	Homozygous state	Develops severe anemia below 2 years, hepatosplenomegaly, blood transfusions dependent	Markedly raised HbF level	Molecular studies

is normal. These mutations are termed as silent mutations such as -101C \rightarrow T, Cap+ 1A \rightarrow C, etc. Causes of normal RBC indices and HbA₂ levels individuals with β -thalassemia trait are given in **Table 4**. Thus it is essential to test for mutation in the spouse of a person who is thalassemia minor for purposes of genetic counseling. Thalassemia minor needs to be differentiated from iron deficiency anemia which is widely prevalent. The parameters to differentiate between these two are given in **Table 5**.

Thalassemia Intermedia

It constitutes heterogeneous group of patients having only mild anemia in absence of other causes of anemia to patients having growth retardation, jaundice (mild to moderate), hemolytic facies (**Fig. 2**), hepatosplenomegaly. These patients may develop iron overload secondary to increased iron absorption because of ineffective erythropoiesis. These patients often have thrombotic and other vascular complication besides complications secondary to iron overload. Course of the disease, complications and management in these cases is different than thalassemia major.

Thalassemia Major

Most babies with thalassemia major manifest in the first year of life and only few in the second year. They often present with varying degrees of pallor, failure to thrive and gain weight, irritability, excessive crying frequent, intercurrent infections, and hepatosplenomegaly (**Fig. 3**). Untreated or poorly treated children develop frontoparietal bossing, hot cross bun appearance of skull, malar prominence, depressed nose of bridge, malocclusion with protrusion of teeth, depressed nasal bridge (**Fig. 4**). X-ray of the skull shows widening of diploid spaces and hair on end appearance (**Fig. 5**). These children may develop osteopenia leading to osteoporosis and pathological fractures of long bones, leg ulcers, gall stones, etc.

Increased iron absorption in response to anemia or transfusional iron through blood often results in multiple endocrine dysfunctions such as pituitary, thyroid, parathyroid and pancreas resulting in various endocrine problems such as diabetes,

Table 5 Differences between thalassemia minor and iron-deficiency

	Thalassemia minor	Iron-deficiency anemia (IDA)
Anemia	Mild	Mild to moderate
Hemoglobin	Slightly low	Low dependency upon severity of IDA
RBC	Raised for Hb level	Decreases with Hb level
MCV	Low	Low
MCH	Low	Low
RDW	Normal	High
Serum iron and ferritin	Normal	Low
TIBC	Normal	High
HbA ₂ level	> 3.5%	< 3.5%

**Figure 2** Child having hemolytic face, protrusion of teeth**Table 4** Causes of normal RBC indices and HbA₂ in β -thalassemia trait

Phenotype	Genotype
Normal RBC indices	α - and β -thalassemia interaction
Normal HbA ₂ levels	Some cases of iron deficiency anemia Silent β -mutations Coinheritance of δ - and β -thalassemia α -globin chain triplication/quadruplication

hypothyroidism, growth retardation, delayed or absent puberty, osteoporosis, etc. Similarly cardiac iron overload along with anemia may result in cardiomegaly, congestive cardiac failure, poor left ventricular ejection fraction intractable arrhythmias, etc. Older children may develop hepatosplenomegaly because of extramedullary hematopoiesis especially in those who are poorly



Figure 3 Child showing the hemolytic face along with hepatosplenomegaly



Figure 4 Picture showing marked facial deformities (depression of nasal bridge, prominence of frontal and maxillary bones, protrusion of teeth and hemosiderosis)



Figure 5 Skull X-ray showing "hair on end" appearance

transfused. Some of these children may develop hypersplenism manifested by increased blood transfusion requirements, leukopenia and or thrombocytopenia. In addition these children may develop transfusion transmitted infections (hepatitis B or C, HIV, etc.) and alloimmunization following multiple transfusions.

MANAGEMENT

Over the years management of thalassemia has evolved from complete cure to supportive care offering near normal life (**Table 6**). Thalassemia monitoring and management are undertaken in day care centers.

Confirmation of Diagnosis

Complete blood counts reveal presence of anemia with peripheral film showing marked poikilocytosis, anisocytosis, microcytic and hypochromic picture with normoblasts target cells, fragmented red

Table 6 Principles of thalassemia management

• Confirmation of diagnosis
• Transfusion therapy to correct anemia
• Treatment of complication of transfusions and transfusion transmitted infection
• Iron overload and chelation therapy
• Splenectomy
• Management of endocrine problems
• Pharmacological therapies to increase gamma chain synthesis
• Curative therapy bone marrow/stem cell transplantation
• Gene therapy

cells (**Fig. 6**) and basophilic stippling (**Fig. 7**). Reticulocyte count ranges between 2% and 4%. MCV and MCH are reduced. Red cell distribution (RDW) is increased. Bone marrow is not essential for diagnosis but it shows erythroid hyperplasia with ineffective erythropoiesis.

Iron studies Serum iron and transferrin saturation are decreased in iron deficiency anemia (IDA), while it may be normal or increased in thalassemia. Total iron binding capacity is increased in IDA and is normal or reduced in thalassemias. Serum ferritin is high in thalassemia.

Hemoglobin electrophoresis Hemoglobin electrophoresis was earlier being done on paper or cellulose acetate membrane. However, with advent of fully automated cation exchange high performance liquid chromatography (HPLC) which is more accurate, reliable efficient methods and is widely used presently. Specific retention windows have been used for identification of various hemoglobin types. Hemoglobin F in untransfused patients varies between 50% and 100% in thalassemia major below 1 year (**Fig. 8**). HbA₂ varies between 2% and 7% depending upon the genotype. Children who have received blood transfusion in them HbF may be low and nondiagnostic. In such cases family studies involving CBC and HPLC will help in establishing the diagnosis.

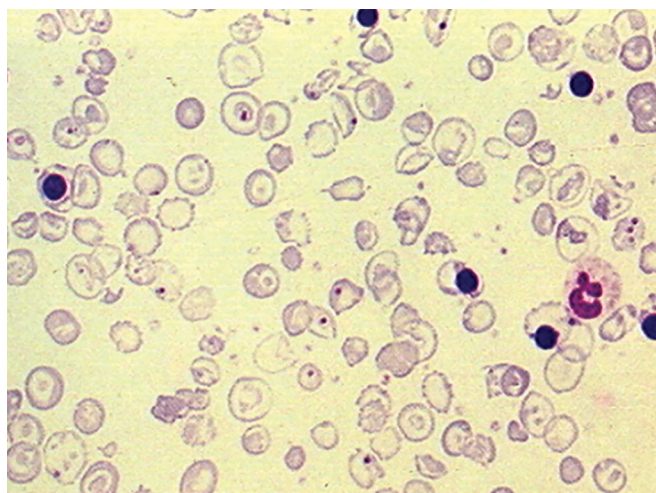


Figure 6 Peripheral blood smear showing anisocytosis, poikilocytosis, microcytic hypochromic picture and nucleated normoblast

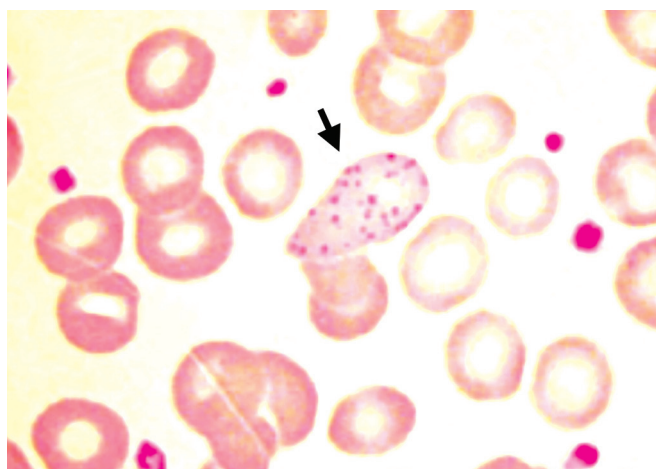


Figure 7 Peripheral smear showing microcytic hypochromic picture with basophilic stippling

F Concentration = 40.0*%

A₂ Concentration = 1.0*%

*Values outside of expected ranges

Analysis comments:

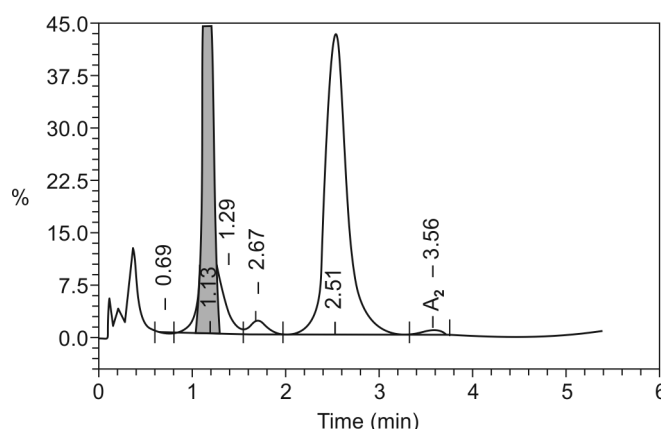


Figure 8 HPLC showing high fetal hemoglobin and normal HbA₂ level

However, in some cases molecular studies may be required to identify the mutation for correct diagnosis. Presently most centers prefer to have molecular studies which are essential for genetic counseling and control of thalassemia in these families.

Transfusion Therapy

The objective of transfusion therapy is given in **Table 7**. Over the years several regimens have been used (**Table 8**). Among these regimens, currently moderate transfusion therapy is being recommended. Initiation of blood transfusion therapy is recommended when Hb falls below 7 g/dL on two occasions done 2 weeks apart in the absence of any concurrent illness and anemia due to other causes. It is preferable to determine the complete genotype of red cells and to transfuse using group and type specific packed red cells which are compatible by direct antiglobulin test to reduce the risk of alloimmunization. It is preferable to transfuse fresh blood (4–5 days old). Currently many centers use prestorage leukodepletion blood for transfusion. In the absence of this facility bedside filters should be used. Generally, 15–20 mL packed red cells/kg should be transfused regularly at 15–25 days interval to maintain pretransfusion hemoglobin between 9.5 g/dL and 10 g/dL. In a normal child blood may be transfused 3–4 mL/kg/hour while in patients with cardiac decomposition it should be given 1–2 mL/kg/hour. All patients should receive hepatitis B immunization before transfusion and thereafter every 5 years. Parents and first degree relative blood should not be transfused in these cases.

Iron Overload

Normally iron is stored in minimal amount as ferritin and hemosiderin which is nontoxic. In thalassemic iron gets accumulated by multiple ways (**Fig. 9**). Initially transferrin gets saturated leading to increase in serum ferritin, free form as non-transferrin bound iron (NTBI) and enters the cell to form labile iron pool (LIP). LIP is an unstable form and releases toxic-free radicals which damage the microsomes, mitochondria, liposomes, various enzyme proteins, etc. The main source of iron overload is secondary to blood transfusion while iron absorption secondary to anemia from diet is minimal in well transfused children. Iron accumulates at different rates in different organs causing organ dysfunctions secondary to toxic form of iron such as NTBI and LIP. Approximate times for development of complications secondary to iron overload in children who are not well chelated are given in **Table 9**.

Table 7 Goals of transfusion therapy in thalassemia

- To obviate the ill effects of hypoxia
- To suppress endogenous erythropoiesis
- To promote normal growth and development and good quality of life
- To prevent complications of under transfusion (hemolytic facies)
- To prevent hepatosplenomegaly
- To ensure safe blood transfusion practices
- To provide transfusion services most suited to patient

Table 8 Types of transfusions regimen in thalassemia

Transfusion regimen	Pretransfusion Hb level (g/dL)
Palliative	8
Moderate	9.5–10.5
Hypertransfusion	10–12
Supertransfusion	> 12

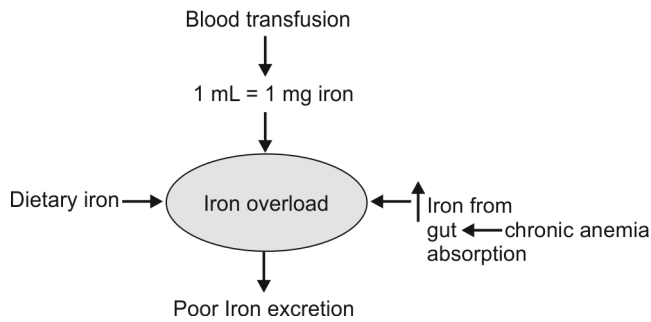


Figure 9 Pathogenesis of iron overload in thalassemia

Table 9 Time for complications in poorly chelated thalassemic children

Increase in serum ferritin	15–20 transfusions
Hepatic fibrosis	3–5 years
Liver cirrhosis	10–15 years
Subclinical cardiac dysfunction	10–12 years
Heart disease	12–15 years
Heart failure	> 15 years
Various endocrine dysfunction	15–20 years

There are several methods of assessing the iron overload. Serum ferritin is simple and has advantage of serial monitoring and well correlates with various organ dysfunctions. Since serum ferritin acts as an acute phase reactant and its level vary greatly in presence of infection stress, etc. It also does not truly reflect various form of iron overload such as NTBI, LIP liver iron concentration (LIC), etc. Recently magnetic resonance imaging (MRI) methods such as spin echo (R_2), single breath hold gradient recalled echo (R_2^*), T_2^* have been used. Superconducting quantum interference device (SQUID) provides state art and is noninvasive method to assess the liver iron stores. It still remains as an experimental tool because of its high cost and availability of few machines in the World. Similarly, NTBI and LIP are being used as research tools. MRI T_2 is being widely used to assess iron overload for liver and cardiac tissue which is given in **Table 10**.

Chelation Therapy

Other important measure is to maintain serum ferritin around 1,000 ng/mL by chelation therapy. Properties of an ideal iron chelator are given in **Table 11**. Presently iron chelators are approved for chelation therapy as given below.

Desferrioxamine (DFO) It is hexadentate produced from *Streptomyces pilosus* and was introduced in 1962. One molecule binds with one iron molecule. It cannot be given orally and has short half-life (5 min). It is able to create negative iron balance when administered in doses of 30–50 mg/kg/day over 10–12 hours either intravenously or subcutaneously with the help of an infusion pump. Long-term chelation therapy in appropriate doses is able to reverse the complications of iron overload such as liver fibrosis, cardiac dysfunction such as arrhythmias, echocardiogram dysfunctions (LVEF), etc. Vitamin C helps to convert Fe^{+++} to Fe^{++} which is chelatable. It should not be mixed with blood; however, it can be given along with blood transfusion through Y-connection. It also chelates zinc, has audiovisual toxicity and delayed linear growth on prolonged use especially when used in higher doses. Side effects of DFO are given in **Table 12**.

Deferiprone deferiprone (DFP) was the first oral iron chelator developed in Hider's laboratory. It is bidentate and water soluble with

Table 10 T_2^* MRI interpretation for hepatic and cardiac iron overload

Liver iron Hepatic T_2^* (ms)	Iron overload	Cardiac iron Cardiac T_2^* (ms)
> 6.3	None	> 20
2.7–6.3	Mild	12–20
1.4–2.7	Moderate	8–12
< 1.4	Severe	< 8

Table 11 Properties of ideal iron chelator

• High affinity for ferric iron form and no/low affinity for other elements (copper, zinc, magnesium)
• High chelating efficiency
• Good tissue and cellular penetration
• To create negative iron balance
• No redistribution of iron
• Safe drug with least side effects
• Oral drug once or twice a day
• Slow rate of metabolism
• Affordable and easily available

Table 12 Side effects of desferrioxamine (DFO)

• Local reaction such as pain, redness, induration
• Retinal and optic nerve dysfunction
• Cataract
• High frequency hearing loss
• Cartilage dysplasia resulting in stunting of growth
• Acute pulmonary toxicity and renal complication in high doses
• <i>Yersinia enterocolitica</i> infection

half-life 1.5–5 hours. It is recommended in dose is between 75–100 mg/kg/day in 2–3 divided doses. It mobilizes iron from transferrin, ferritin and hemosiderin. It has better penetration within the cells. It does not chelate other elements and has no ill effects on eyes, ears and on growth and development. It chelates iron more effectively from heart than DFO. Few children develop gastrointestinal symptoms like nausea, vomiting and abdominal pain. Nearly 15–20% of children develop joint pain and some of them progress to arthropathy. This complication is more frequent in children with higher serum ferritin levels. Neutropenia occurs in less than 1% of cases and thus CBC should be done regularly. Drug should be stopped during febrile episodes and should be started once CBC is normal.

Shuttle hypothesis Deferiprone being smaller molecule enters tissue cells more easily and is able to bring DFP and iron complex into plasma where DFO with stronger affinity binds with iron molecules and excretes the DFO iron complex more effectively. DFO in different regimens has been used in dose of 30–50 mg/kg twice or thrice a week while DFP (50–75 mg/kg) has been used daily. Combination therapy (DFO and DFP) is recommended in patients with high serum ferritin or children with any cardiac, hepatic or endocrine complications due to iron overload to reduce serum ferritin rapidly without much toxicity.

Deferasirox Deferasirox (DFX/ICL670) is a tridentate molecule with high specificity for iron, and was approved in 2005. It has half-life of 12–18 hours and thus given once a day orally dissolved

in water or juice (orange/apple). It is started in dose of 20 mg/kg/day and dose can be increased to 40 mg/kg/day. It is a total body iron chelator and excretion of iron is dependent on dose and serum ferritin levels. Its side effects are minimal which include skin rashes, nausea, vomiting, abdominal pain, headache, fatigue, skin pigmentation. Transient rise in liver enzymes, blood urea and serum creatinine have been observed. Recently DFX has been used in combination with DFO and been shown to have synergetic effect. Phase II Hyperion study in smaller number of cases has shown that combination therapy is safe and more effective.

Newer iron chelators which are under trial include hydroxyethyl starch (HES). DFO having longer half-life and deferitin another tridentate chelator belonging to ferrothiocin class. Folic acid is cheap and safe should be given to all to prevent its deficiency.

Monitoring

All children require regular monitoring as recommended in **Table 13**. Primarily to prevent development of any complication and to detect the complication early and institute appropriate therapy.

Hypersplenism

It usually occurs secondary to inadequate transfusion, development of alloimmunization, chronic liver disease, etc. Indications of splenectomy are given in **Table 14**. It should not be undertaken in children below 5 years of age. All patients undergoing splenectomy should receive pneumococcal, *Haemophilus influenzae*, meningococcal vaccine 4 weeks prior to surgery. These children should also receive *Salmonella typhi* and other vaccines regularly. Lifelong oral penicillin prophylaxis is recommended. These children should be advised to start ciprofloxacin at start of febrile episode at home and

Table 13 Monitoring of children with thalassemia

Each visit
• Complete blood counts (CBC)
• Weight, height on growth charts, liver and spleen size
• Adverse reaction of blood transfusion, if any
Three monthly
• Urine analysis
• Liver and renal function
• Serum ferritin
Yearly
• Annual blood transfusion requirement
• Hepatic serology (HbsAg Anti HCV/HIV)
• T ₂ MRI for cardiac and iron overload
After 10 years (yearly)
• ECG, echocardiography
• Endocrine (e.g., for thyroid, hypoparathyroid, diabetes)
• Bone mineral density, 25 hydroxy vitamin D3 level
• Sexual development (LH, FSH, testosterone, Tanner staging)

Table 14 Indication of splenectomy in thalassemia

• Packed red cell requirement exceeds 200 mL/kg/year
• Annual packed cell transfusion 1.5 times of basal requirements
• Difficult to maintain pretransfusion Hb level of 10 g/dL
• Massive spleen size with or without abdominal discomfort or pain
• Presence of leukopenia or thrombocytopenia

Table 15 Risk factors and outcome of bone marrow transplantation

Risk factors	Class	Overall survival (%)	Thalassemia free survival (%)
Hepatomegaly > 2 cm	I. Absence of all risk factors	94	87
Liver fibrosis	II. Presence of one or two factors	84	81
Irregular chelation (high serum ferritin level)	III. Presence of all three factors	70	58

should report to doctor for appropriate treatment at the earliest possible. Thrombocytosis may occur following surgery and aspirin (75 mg/kg/day) should be administered as long as platelet counts are more than 800,000/mm³.

Fetal Hemoglobin Inducer

Several drugs such as 5-azacytidine, butyrate, decitabine, EPO and hydroxyurea either singly or in combination have been used to increase the fetal hemoglobin to decrease the imbalance between alpha globin versus nonalpha globin chains. Among these drugs hydroxyurea is most promising and has been found to improve the hemoglobin levels in following indications:

- $\delta\beta$ -thalassemia
- β -thalassemia intermedia homozygous for XmnI polymorphism
- Patients with hypercoagulability, pulmonary hypertension, leg ulcers
- Extramedullary hematopoiesis or pseudotumors
- Alloimmunized children requiring frequent blood transfusion.

This drug is well tolerated given in dose of 10 mg/kg/day and it should be gradually increased to maximally tolerated dose of 20 mg/kg/day. Folic acid supplementation is essential. Response usually occurs within 6 months of therapy.

Curative Therapy

Replacement of bone marrow stem cells with normal fully HLA matched hematopoietic stem cell will correct the underlying defect and thus offers complete cure. This has been possible over the last 3–4 decades using stem cells from bone marrow and process is called bone marrow transplant (BMT) hematopoietic stem cells from blood (HSC Transplant), cord blood (CB Transplant). Source of stem cells from sibling donor has much better results. The probability of sibling donor match availability is around 30%. Thus few centers have initiated unrelated BMT or HSCT program after finding an appropriate match through various bone marrow registries. Lucarelli and his colleagues have identified the risk factors (**Table 15**). Any child who is between 2–5 years, well chelated (serum ferritin around 1,000 ng/mL) and has fully matched sibling donor is best suited for transplant. With the improvement in conditioning regimens and management of graft versus host disease, the long-term results of BMT have improved significantly.

Thalassemia Screening and Control

Since thalassemia is inherited disorder it can be controlled by screening and control program. Few countries in the world have controlled the birth of thalassemia. It is possible by preventing the marriage between two carriers by screening and confirmation test. RBC indices (MCV < 78 fL/MCH < 27 pg with RBC count high for Hb levels), positive nestro test are suggestive of carrier state. These are simple and cheap mass screening test. Persons with positive screening test should be confirmed by Hb electrophoresis (HPLC) with HbA₂ > 3.5%. In the general population, the birth of thalassemia can be prevented by genetic counseling. Secondly, all women during their first antenatal check-up should be screened for thalassemia carrier and those who are positive on screening test need to undergo confirmatory test by HPLC. Husband of thalassemia carrier women need to undergo HPLC test to identify the couples at risk. Molecular studies are undertaken on couples at risk to identify the mutations. During 10–12 weeks of gestation

chorionic villus sample is taken to identify the affected fetus which is aborted to control the birth of thalassemia. The success of national program lies on mass awareness, commitment of medical profession and social organizations besides very strong political will.

IN A NUTSHELL

1. Nearly 4% of world's population is affected by thalassemia which is the most common hemoglobin disorder.
2. The molecular basis of alpha and beta thalassemia is well identified.
3. The clinical picture depends on thalassemia mutations along with the primary, secondary and tertiary modifiers.
4. Individuals with thalassemia minor are asymptomatic while children with thalassemia major present with severe anemia, and hepatosplenomegaly in the first year of life.
5. The principles of management include: (a) confirmation of diagnosis, (b) to maintain hemoglobin at 10 g/dL by repeated pack cell transfusions, (c) to maintain serum ferritin are around 1,000 ng/mL by chelation therapy.
6. All effort should be made to achieve the desired serum ferritin level by use of desferrioxamine, deferiprone and deferasirox either single or in combination.
7. Precautions should be taken to prevent the complications of disease and therapy.
8. Thalassemia can be prevented by screening and control methods.

MORE ON THIS TOPIC

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Chapter 38.11

Sickle Cell Disease

Vibhawari S Dani, Dipty Jain

Sickle cell disease (SCD) is the most common hemoglobinopathy worldwide. It was first described by Herrick in 1910. Pathological basis of hemoglobin (Hb) molecule was defined by Hahn and Gillespie in 1927. The presence of sickle Hb was first described in India in 1952 in the tribal populations of Nilgiri hills in South India by Lehman. SCD is a monogenic disorder with considerable clinical diversity. SCD is a term used for a group of genetic disorder characterized by production of hemoglobin 'S' (HbS). Sickle cell hemoglobinopathy occurs due to mutation of β -globin gene situated on short arm of chromosome 11, where adenine is replaced by thymine in base of DNA coding for the amino acid in the 6th position in β -globin chain. This leads to an amino acid change in β -chain of Hb molecule, from glutamic acid to valine. The substitution of single amino acid is responsible for profound change in molecular stability and solubility of HbS. Minor variations in noncoding nucleotide sequence of genes are also seen. The polymorphic variations are called haplotypes. Four such haplotypes have been found. Arab-Indian haplotype is found in Eastern Saudi Arabia and Indian subcontinent, Bantu haplotype is prevalent in Central African Republic, Benin haplotype is prevalent in Central West Africa, Mediterranean countries, Northern and Southern American countries, Senegal haplotype is prevalent in Atlantic West Africa.

EPIDEMIOLOGY

Sickle cell disease is prevalent in populations that evolved in moderate and humid climates where malaria was endemic. Heterozygous sickle cell trait offers relative protection to malaria in comparison to normal population. This may be due to decreased invasion of parasite in the red cell due to cell wall rigidity, failure of parasite to grow within red cell, increased phagocytosis of infected red cells. SCD is particularly common among people having ancestral origin from sub-Saharan Africa, India, Saudi Arabia and Mediterranean countries. In broad term, the prevalence of the sickle cell trait, i.e., healthy carrier who has inherited the mutant gene from one person only, ranges between 10% and 40% across equatorial Africa, in West African countries such as Ghana and Nigeria the frequency of trait is 15–20%.

Prevalence of SCD in North-East India is 0 to 20%, Central India 22 to 44%, Western India 0 to 33% and South India 0 to 40% (Fig. 1). Nearly 20 million people are affected in India. The sickle cell gene is predominantly seen among tribal population in India, many of whom live in remote hilly regions. It is also prevalent among schedule castes and other backward classes who are economically disadvantaged. Children from India where the sickle gene is linked to the Arab-Indian haplotype are stated to have a milder disease than those with African haplotypes. However, a study from Central India has reported severity of homozygous SCD to be at par with African haplotypes.

SICKLE CELL SYNDROMES

The term SCD includes several distinct genotypes:

- Homozygous sickle cell disease (SS)— $\alpha_2\beta_2^{\text{val } 6}\alpha_2\beta_2^{\text{val } 6}$
- Heterozygous sickle cell disease (AS)— $\alpha_2\beta_2^{\text{val } 6}\alpha_2\beta_2^{\text{Glu } 6}$. This is a benign condition. There is no anemia or decreased red cell survival.

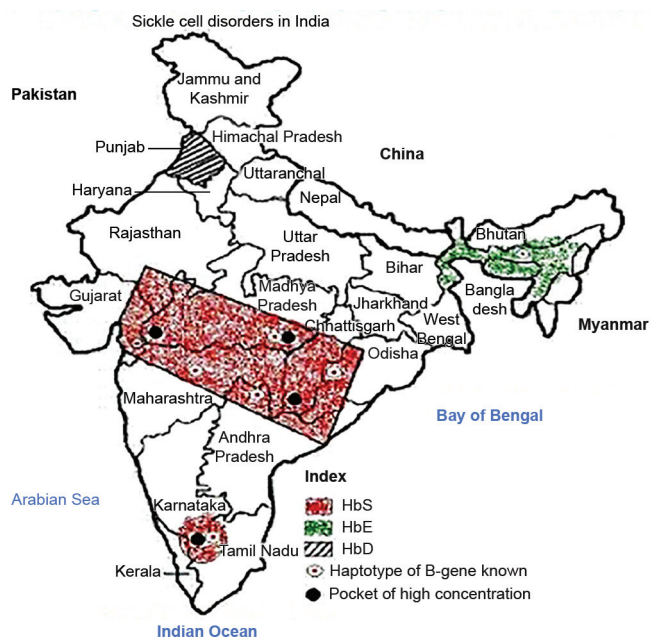


Figure 1 Prevalence of sickle cell gene in India

- Sickle- β -thalassemia—Clinical severity depends on output of thalassemic β gene.
- Less commonly seen forms are:
- SD Punjab disease— $\alpha_2\beta_2^{\text{val } 6}\alpha_2\beta_2^{\text{Glu } 121}$. It has severe clinical presentation.
- SO Arab disease— $\alpha_2\beta_2^{\text{val } 6}\alpha_2\beta_2^{\text{lys } 121}$. It has severe clinical presentation.
- SC disease $\alpha_2\beta_2^{\text{val } 6}\alpha_2\beta_2^{\text{lys } 6}$. It has milder clinical presentation than sickle cell disease.
- Sickle α -thalassemia.

PATHOPHYSIOLOGY

Hemoglobin is normally present in the soluble (Sol) form in the red blood corpuscle (RBC). The Sol form of Hb changes to Gel form, when 'HbS' is polymerized on deoxygenation. In gel form Hb is crystallized to small rigid boat shaped object known as tactoids. These tactoids polymerize forming insoluble fiber like structures, deforming RBC to sickle shape. The polymerization is facilitated by hypoxia, decreased pH, decreased 2,3-diphosphoglycerate (2,3-DPG) concentration and increased carbon monoxide concentration. On re-oxygenation the red cells initially resume normal configuration, but membrane damage is pronounced with repeated cycles of sickling and unsickling resulting in the fixation of membrane in sickle configuration leading to irreversible sickle cell formation and hemolysis. This hemolysis is responsible for anemia in SCD. Life span of sickle red cell is 8–21 days.

Mechanism of Membrane Damage

Red cell membrane associated 'HbS' leads to formation of spectrin-hemoglobin complex, which leads to erythrocyte rigidity. Auto oxidation of 'HbS' generates potent oxidants, e.g., superoxide, peroxide and hydroxyl radicals causing oxidative damage of red cell membrane. In SCD red blood cells have normal shape and normal viscosity when oxygenated, which allows them to slip into microvasculature, where these red cells become deoxygenated leading to distorted shape and become viscous, they cause blockage of microvascular circulation and formation of irreversible sickle cells. This is Trojan horse phenomenon.

Increased Red Blood Cell Adhesion to Endothelium

In SCD the red cells have increased adherence to endothelium. The red cells assume sickle shape after deoxygenation and damage the endothelial cells leading to subendothelial infiltration and narrowing of vessels. Leukocytes, platelets aggregate over the adherent red cell damaged endothelium causing blockade and ischemia of tissue. CD44 and integrin present on red cell membrane adhere to fibronectin and endothelial protein vascular cell adhesion molecule-1 (VCAM-1). Leukocytes adhere to intercellular adhesion molecule-1 (ICAM-1), and E-selectin present on endothelium.

Coagulopathy

It is known that patients with SCD present with activation of the blood coagulation and fibrinolytic systems, especially during vaso-occlusive crises and also during the steady state of the disease. The presence of mutation of the factor prothrombin gene (*G20210A*) variant, factor V gene (*G1691A*) and polymorphism of factor V Leiden, methylenetetrahydrofolate reductase (*MTHFR*) (*C677T*) may be risk factors for vascular complications in individuals with SCD.

Deregulation of Nitric Oxide Metabolism

Nitric oxide stimulates cGMP, and decreases smooth muscle calcium concentration. This causes muscle relaxation, vasodilatation and increase in regional blood flow. It also reduces adherence of endothelium and suppresses platelet aggregation.

Nitric oxide levels are depleted in SCD due increased reactive oxygen species, i.e., oxidants, denatured 'HbS', damage to red cell membrane, microvascular blockage causing tissue ischemia. There is increased free plasma Hb which consumes thousand times more nitric oxide than intracellular Hb.

CLINICAL MANIFESTATIONS

Clinical manifestations of SCD are extremely varied. Some patients are entirely asymptomatic whereas other patients are constantly troubled by painful episodes. The clinical picture in most patients falls between these two extremes.

Sickle Cell Crisis

The term sickle cell crisis was defined by Diggs as *any new syndrome that develops rapidly in patients with sickle disease due to inherited abnormality*. There are three categories of sickle crisis—vaso-occlusive crisis leading to painful episodes, sequestration crisis, and aplastic crisis.

Vaso-occlusive Sickle Cell Crisis

Vaso-occlusive crisis are acute painful episodes due to intravascular sickling and tissue infarction. Vaso-occlusive episode are major clinical manifestation of SCD and occur most commonly in bones, lungs, liver, spleen, brain, and penis.

Acute Painful Episode

This is the most common clinical feature of vaso-occlusive crisis. There is typically rapid onset severe deep throbbing pain, usually without any abnormal physical or laboratory finding but sometimes accompanied by local tenderness, erythema, warmth and swelling. The underlying pathologic cause is bone marrow ischemia, sometimes leading to frank infarction with acute inflammatory infiltrate. Lumbosacral spine, juxta-articular areas of joints like knee, shoulder, and elbow are most commonly involved. Precipitating factors for acute painful episodes are exercise, infection, dehydration, psychological stress, low fetal Hb ('HbF').

The treatment consists of medication for pain relief, rehydration and reassurance. Resolution is usually complete.

Hand and Foot Syndrome

In children younger than 5 years of age small bones of hands and feet are often affected. This painful *hand-foot syndrome* is typically the first clinical manifestation of SCD. Diagnosis is done by characteristic clinical appearance (**Fig. 2**). Involvement varies from individual bone to multiple small bones of hands and feet. Unilateral dactylitis should be differentiated from osteomyelitis because treatment differs significantly. Dactylitis requires pain medications such as acetaminophen with codeine, whereas osteomyelitis requires at least 6 weeks of antibiotics. Hand and foot syndrome disappears when bone marrow from small bones of hands and feet stop erythropoietic activity. The age at which a child experiences the *hand-foot syndrome* is strong predictor of overall severity by 10 years of age. These episodes resolve completely but attacks tend to recur.

Pain in Bones

Several ribs are affected with painful swelling. There is pleuritic pain on deep breathing. This may lead to secondary hypoventilation. Avascular necrosis of bone occur secondary to vaso-occlusion of nutrient artery. Femoral head, humerus, upper part of tibia can be affected but weight bearing makes femoral head necrosis more likely to cause severe disability. Most commonly occurs in adolescents and young adults. Persistent pain in hip joint is often associated with limp and painful limitation of movements (**Figs 3 and 4**).

Painful Abdominal Crisis

This occurs due to localized areas of bowel dysfunction. Its exact cause is unknown, although mesenteric vessels occlusion and vertebral diseases with nerve root compression have been suggested. There is severe abdominal pain associated with vomiting, abdominal distention, diminished bowel sounds. X-ray in standing position shows dilated bowel loops and fluid levels. The conservative management includes bowel rest and maintenance of hydration, pain relief. It usually resolves in 2–4 days, however it may recur.

Acute Central Nervous System Event

Among children with SCD, approximately 10–20% will have either overt or silent stroke respectively before 18 years of age. Incidence is estimated to be 0.7% per year during first 20 years of life, with highest rate in children 5–10 years of age. This complication



Figure 2 Dactylitis in sickle cell disease



Figure 3 Avascular necrosis of humerus



Figure 4 Avascular necrosis of head of femur

may occur in isolation but also appears in setting of pneumonia, aplastic crisis, viral illness, painful crisis, priapism or dehydration. The most common underlying lesion is internal carotid stenosis or obstruction but proximal medial carotid artery and anterior carotid artery are also involved. In the cerebral blood vessels, chronic damage to endothelium occur due to sickled red cells resulting in proliferation of fibroblast and smooth muscle, aggregation of leukocytes and platelets over damaged endothelium leading to stenosis. Thus, acute sickling may be the last precipitating event causing acute infarction in chronically damaged, already injured, and stenosed blood vessels. Hemiplegia, speech defect, seizures, and gait dysfunction occur.

Best initial diagnostic test is CT scan. But it is limited by not being able to pick up lesion in first 4–6 hours where MRI can be the investigation of choice. Oxygen is administered to maintain SPO_2 above 96%. Blood transfusion within 1 hour of presentation, with goal of increasing Hb to maximum of 11 g/dL is effective. If baseline Hb is more than 11 g/dL, then standard approach is exchange transfusion to reduce 'HbS' by at least less than 50% if not 30%. The maintenance blood transfusion program for secondary prevention of stroke should be considered to keep Hb level at 11 g/dL.

Primary prevention of stroke Transcranial Doppler assessment of blood velocity of internal carotid artery and proximal portion of middle carotid artery is done. Maintenance transfusion therapy to maintain 'HbS' less than 30% can be considered in those children with time averaged blood velocity of more than 200 m/s. This results in 85% reduction in the rate of overt strokes.

Intracranial Hemorrhage

It is also major category of sickle cell related events. Many of these episodes are subarachnoid hemorrhage from small bleeding aneurysm that probably arise from internal damage.

Priapism

Priapism is persistent painful penile erection. Highest incidence is in children between 2 years and 4 years. Recurrent priapism manifests with episode lasting for few minutes to several hours. It most commonly occurs around 4 am during sleep or soon after waking. It usually subsides spontaneously. If pain, engorgement persists for 24–48 hours, blood transfusion is indicated. Impotency may be a sequel. Prevention is done by oral stilbestrol 5 mg daily, gradually tapered and omitted over a period of 2 months.

Acute Chest Syndrome

These are episodes of acute lung injury with radiographic evidence of infiltrate and are usually accompanied by pleuritic chest pain, fever, cough, tachypnea and hypoxia. This is leading cause of morbidity and mortality in children and occurs more commonly in children under two years. In most cases the etiology is not clearly defined enough to allow prevention. Infection, infarction, acute pulmonary sequestration, etc. are contributory components.

Management Broad spectrum antibiotic coverage is advised. Oxygen therapy is important in hypoxic patient. PO_2 of less than 75 mm Hg indicate poor prognosis. Transfusion is critical for patient with persistent hypoxia. Exchange transfusion is indicated if hematocrit is high. Preliminary evidence inhaled nitric oxide may be of benefit in severe hypoxia.

Anemia

Anemia is due to chronic hemolysis and is very commonly associated with nutritional deficiency including folate and iron deficiency. The other causes of severe anemia are acute splenic sequestration, aplastic anemia, anemia due to infection and chronic hypersplenism.

Acute Splenic Sequestration Crisis

The event is characterized by sudden trapping of large amount of red cell mass in spleen or less commonly in liver and sudden, rapid, massive, enlargement of spleen. Patients become weak, dyspneic with rapidly enlarging spleen, anemia and shock. The hematocrit becomes half the patient's usual value within few hours. There is associated brisk reticulocytosis to 20–30%, with increased nucleated RBCs and moderate to severe thrombocytopenia. Occurrence is most common between 3 months and 5 years of age but rarely may occur in adults with persisting splenic tissue. Splenic dysfunction occurs due to obstruction of sinusoidal blood flow, leading to diversion of blood through intrasplenic shunts, bypassing phagocytic reticuloendothelial element of the spleen. Sequestration may recur within 4 months of initial episode. Blood transfusion is required in emergency but care must be taken as Hb level can exceed calculated amount as pooled blood may be thrown in circulation. To eliminate recurrence, elective splenectomy after second episode is recommended. Pneumococcal vaccine and prophylactic penicillin for 3 years is recommended following splenectomy.

Aplastic Crisis

This event associated with temporary cessation of bone marrow activity affecting predominantly the red cell precursors, due to suppression by intercurrent viral or bacterial infection. Parvovirus B19 is most commonly associated organism. The child presents with, severe anemia, having Hb 2–4 g/dL, without compensatory reticulocytosis. Reticulocytes are 0% during crisis, however there is daily marked increase consistent with recovery phase. Any child of SCD with reticulocytopenia should be considered as having parvovirus B19 infection until proven otherwise. Occurs in epidemics, mostly affects children below 15 years of age. Treatment requires packed red blood cell transfusion. Daily monitoring of reticulocyte count should be done.

Acute infection with parvovirus B19 may be associated with fever, pain, splenic sequestration, acute chest syndrome (ACA), glomerulonephritis, and stroke.

Chronic Hypersplenism

There is red cell sequestration in spleen, associated with marked splenomegaly. It is most common between ages of 5 years and 15 years and presents with marked anemia, gross splenomegaly and growth retardation. Gradual lowering of Hb below steady state level occurs usually over a period of few months. Hb level is maintained by blood transfusions. Splenectomy may be required if resolution does not occur in 6 months.

Jaundice

Mild or moderate jaundice is due to chronic hemolysis leading to high bilirubin load. Severe jaundice could be due to cholestasis, viral hepatitis or sickle hepatopathy. Cholestasis is due to high bilirubin load caused by hemolysis. Risk of viral hepatitis is increased because of frequent transfusions. G6PD deficiency, if present may be an added component leading to deep jaundice. Cholecystitis presents with pain in right upper quadrant, vomiting, fever and positive Murphy's sign. Ultrasound shows thick edematous gallbladder. Gallstones may be associated. Gallstones are formed due to high bilirubin excretion secondary to accelerated hemolysis. They may be multiple. Gallstones, if symptomatic, should be removed by endoscopic retrograde cholangiopancreatography (ERCP) or cholecystectomy. Hepatic sequestration, seen uncommonly, presents with liver enlargement, tenderness, very high bilirubin levels and abnormal liver enzyme concentration. Acute intrahepatic cholestasis, an uncommon complication may cause deep jaundice.

Infection

Infection is the most common cause of morbidity and mortality in children with SCD. The major risk factor for increased vulnerability to infection is splenic dysfunction, which leads to appearance of RBCs with *Howell-Jolly bodies* and irregular surface characteristics *pits*. When percentage of pitted RBCs exceeds 3.5%, the spleen is generally nonfunctional. Other risk factors are defective alternative pathway for complement-mediated lysis due to deficient levels of serum opsonin and abnormal production of antibodies. In young children, risk of pneumococcal sepsis is approximately 400 times that of normal children and *H. influenzae* sepsis appears to be 2–4 times common. Organisms most commonly involved are *Streptococcus pneumoniae*, and *H. influenzae*. Osteomyelitis is most often caused by *Salmonella*. High grade fever (> 39°C or 102.4°F) is potentially serious in children with homozygous 'SS' disease and possible septicemia must be investigated. *Streptococcus pneumoniae* is widely recognized but *H. influenzae*, *Staphylococcus*, *Klebsiella*, *Salmonella* are also important contributory factors. These children should be managed with intravenous third-generation cephalosporins. Prophylaxis with oral penicillin, erythromycin up to 5 years of age and pneumococcal vaccination is advised.

Chronic Organ Damage

Cardiovascular system Abnormal cardiac findings in most patients with sickle cell anemia are primarily due to chronic anemia and compensatory increased cardiac output. Cardiomegaly is found in most of the patient. Pulmonary hypertension is the most severe cardiovascular complication.

Renal system Sickle cell nephropathy includes papillary necrosis, nephrotic syndrome, renal infarction, hyposthenuria, pyelonephritis and renal medullary carcinoma. The presentation of these entities could be hematuria (microscopic or gross), proteinuria, renal insufficiency and urine concentrating defects.

Hepatobiliary system Hepatobiliary complications include cholelithiasis, hepatic infarction and transfusion related hepatitis.

Leg ulcers They are typically chronic ulcers around malleoli or shin of tibia. They have well demarcated border and surrounding skin is often hyperpigmented and indurated. Management includes cleaning the wound, with mild antiseptic wet dressing. Antibiotics have no role. Oral zinc sulfate improves healing. It is not a very common presentation in India.

Eyes Tortuosity and loculation of conjunctival vessels are seen. Sickle cell retinopathy includes proliferative and nonproliferative retinopathy which can lead to vitreous hemorrhage and retinal detachment.

Growth Somatic and sexual growth is delayed in SCD. Age of menarche is delayed by 2.5 years. Zinc deficiency has been suggested as a cause for poor growth. It has been observed that zinc supplementation augments sexual growth but does not affect somatic growth.

Enuresis It is common in SCD. It is probably secondary to hyposthenuria, associated with small bladder capacity up to 8–10 years of age. Eventually it always resolves.

GENETIC MODIFIERS

Remarkable heterogeneity in clinical severity is observed in homozygous sickle mutation. Genomic mapping has shown various aberrations associated with sickle mutation, responsible for variability in clinical picture. Genes that modulate hemolysis, vasoregulation, cell adhesion, oxidative stress and inflammation play role in clinical manifestation of severity of SCD. Genetic manifestations are associated with clinical complications; however expression of such association is variable. There can be variations in genes known to be associated with certain clinical condition, e.g., stroke, avascular necrosis of bone, priapism, elevated levels of 'HbF', leg ulcers, renal failure that coexist with sickle cell mutation.

Structural changes in β -globin gene like nondeletion mutation ($^G\gamma$ -C158→T) that increases 'HbF' level is associated with Indian Arab and Senegal β -globin haplotype. Locus for production of red cell with 'HbF' is on short arm of chromosome Xp22-23. It accounts for variations in 'HbF' levels in SCD. Other loci on chromosome 8, 6q22.3 are involved in base line maintenance of 'HbF'. Loci on chromosome 1, 12, 13 determine 'HbF' response to hydroxyurea therapy. Genetic mutations may be in the form of deletions in the globin gene region.

Hemoglobin F

Hemoglobin 'F' level in SCD may vary from 0.5% to 30%. 'HbF' reduces polymerization of 'HbS' molecule, thereby reduces severity of clinical picture. 'HbF' is heterogeneously distributed in red cells. Number of red cells with 'HbF' and amount of 'HbF' in red cells also varies in individuals. This results in variable preferential survival of 'F' cells over 'non-F' cells.

Alpha Thalassemia

It is due to structural variation, deletion and altered number of α -thalassemia genes. Primary effect of alpha thalassemia is to reduce the cellular content of 'HbS'. There is microcytosis. Reduction in mean cell hemoglobin concentration (MCHC) prolongs the time required for 'HbS' polymerization. The red cells are more deformable, less rigid and have greater ratio of membrane surface area to volume. Life expectancy is increased in association of alpha thalassemia with SCD. However, there is no protection from stroke, and increased incidence of avascular necrosis of femur is observed.

DIAGNOSIS

Community Screening

Community screening for SCD can be done by sodium metabisulfite slide test and solubility test. These are screening test and cannot differentiate between sickle cell trait and disease. These tests should not be used in first year of life as high level of 'HbF' is present. Confirmation is done by Hb electrophoresis, isoelectric focusing, high-performance liquid chromatography (HPLC), globin DNA analysis, etc. Diagnostic test for SCD should not be done within 3 months after receiving blood transfusion.

Prenatal Diagnosis

Chorionic villus biopsy or amniocentesis are procedures done at 8–12 weeks and 12–18 weeks respectively for prenatal diagnosis of SCD. After 18 weeks cordocentesis can be done but with a higher risk as compared to other two procedures. Polymerase chain reaction (PCR) technique is applied for amplification of DNA. (a) ARMs, i.e., amplified refractory mutations and b) CRDB, i.e., covalent reverse dot blot hybridization techniques are used.

Neonatal Screening

All newborns from high-risk population should be screened for SCD. SCD fulfills all criteria for neonatal screening since with early detection and comprehensive health-care; life expectancy of children having SCD can be increased with significant reduction in morbidity. Blood is obtained from umbilical cord or heel prick. Dried samples on filter paper may be sent to central laboratory for HPLC analysis. If newborn screening shows 'F' and 'S' hemoglobin with baseline hemoglobin range between 6 g/dL and 12 g/dL, the diagnosis is likely to be homozygous SCD or sickle β -thalassemia. In newborn, if screening shows hemoglobin analysis of 'F', 'A', 'S' hemoglobin the diagnosis is likely to be heterozygous SCD or sickle cell trait. Reconfirmation of diagnosis is advisable at 6 months by HPLC preferably along with molecular studies.

Investigations

Children of SCD should be under regular follow-up. Periodic investigations should be done. Complete blood count (CBC), reticulocyte count should be done every 3 months, liver and renal function studies should be done initially as baseline and later yearly, ophthalmic check-up once a year, carotid Doppler once a year, ultrasound for gallstones once a year should be done.

MANAGEMENT

Patients with SCD should be followed on routine basis. Patient and his family should be educated about the nature, course, treatment and its complications of the disease.

Prevention of Crisis

Exposure to hypoxia, dehydration, extreme cold, extreme heat, change in altitude, infections are precipitating factors for crisis. They should be avoided. Dehydration and loss of electrolytes may

lead to red cell dehydration precipitating sickling process. In our tropical country plenty of fluids should be taken regularly. Parent's education for recognizing specific complication at the earliest, should be done. Immunization should be done with pneumococcal conjugate vaccine at age of 6, 10 and, 14 weeks, booster at 18 months should be followed by polysaccharide (23 valent) pneumococcal vaccine after 2 years; Influenza (Hib) vaccine should be given at 6, 10, 14 weeks and booster at 18 months; Typhoid vaccine; Hepatitis B vaccines, at birth, 6 weeks, 6 months, booster every 5 years.

Prophylactic penicillin should be given to all children younger than 5 years (125 mg BD until the age of 3 years and, 250 mg BD after 3 years). Hemoglobin levels should be maintained at 10–12 g/dL. Folate supplementation should be given, as there is rapid turnover of bone marrow. Dose is 2.5 mg/day below age of 5 years and 5 mg/day above age of 5 years.

Pain Management

Painful events are usually treated with adequate hydration and analgesics. Early intervention of acute painful episodes should be done with oral analgesics at pain start point to cut-off the pain cycle. Fluid requirement is usually increased by 50% of the usual requirement during crisis. For mild pain—codeine, aspirin, ibuprofen, acetaminophen, naproxen, can be used. For severe pain—meperidine, ketorolac, tolmetin, oxycodone, etc., are useful. Vasodilators like pentoxifylline, nifedipine, and buflomedil increase microvascular circulation.

Hydroxyurea

Hydroxyurea is myelosuppressive agent, which is the only effective drug proved to reduce painful episodes and ameliorate the severity of SCD. It acts by increasing 'HbF' level, improving rheological properties by decreasing adhesiveness and absolute number of neutrophils and reticulocytes. It also decreases hemolysis by improving hydration of red cells, hampering sickling mechanism. It is started for the following indications: (A) child more than 5 years of age with admissions for painful episodes more than three in a year; (B) History of more than three blood transfusions in a year; (C) Single episode of acute chest syndrome; (D) Stroke; and (E) Avascular necrosis of bone.

Dose Starting dose is 15–20 mg/kg with an incremental dose increase every 8 weeks of 2.5–5 mg/kg if no toxicity occurs, up to a maximum of 35 mg/kg. Strict monitoring for hematological toxicity by CBCs, reticulocyte count should be done every 2 weeks. In Indian setup it is found that fixed low dose of 10–15 mg/kg without escalating is as effective as the recommended schedule.

Blood Transfusion

Patients with SCD tolerate chronic anemia well and may require transfusion in sequestration crisis, CNS infarction, aplastic crisis, preoperative, and hypoxia with acute chest syndrome. A standard simple transfusion in necessary in sequestration crisis and aplastic crisis, while in all other situation exchange transfusion is preferable. All compensated anemia do not require blood transfusion. Chronic transfusion program is used in children with recurrent stroke, to reduce number of 'HbS' containing cells. Autologous bone marrow transplant has been found successful in very severe SCD.

Bone Marrow Transplant

Bone marrow transplant with HLA compatible hematopoietic stem cells is done with good results.

Gene Therapy

It is still in experimental stage. Random insertion of normal β gene, or correction of the defective gene by genetic engineering in hematopoietic cell is still on horizon.

Behavior Change Communication for Prevention

Sickle cell disease is an autosomal recessive disorder. To prevent birth of homozygous SCD, multipronged community awareness approach is needed. Mass screening of marriageable youth for SCD and premarital counseling should be done. A carrier, i.e., sickle cell trait should not marry heterozygous or homozygous SCD.

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IN A NUTSHELL

1. Sickle cell disease has autosomal recessive transmission. It has high prevalence in some areas with high-risk communities. It has high morbidity due to infection, pain, anemia, jaundice.
2. Cheaper simple screening tests like solubility test and sodium metabisulfite test are available, but for confirmation of diagnosis Hb electrophoresis is required.
3. Newborn screening program can reduce morbidity. Prenatal diagnosis facilities are available. Community awareness needs to be created.
4. High levels of hemoglobin 'F'; co-inherited alpha thalassemia have milder clinical course.
5. Common causes of death are pneumococcal septicemia, acute splenic sequestration and acute chest syndrome. Pneumococcal vaccine and penicillin prophylaxis can reduce mortality.
6. Nutritional correction of deficiency of iron and folate is important in management of anemia.
7. Analgesics at pain start point are important in cutting off pain cycle and improving quality of life. Hydroxyurea reduces painful crisis, acute chest syndrome. Bone marrow transplant has promising result. Premarital counseling can prevent SCD.
8. Chronic blood transfusion program reduces recurrent stroke.

Chapter 38.12

RBC Membrane Defects

Nitin Shah, Khushnuma Mullanfroze

Hemolytic anemias due to abnormalities of the RBC membrane are an important group of hematological disorders. These include hereditary spherocytosis (HS), hereditary elliptocytosis (HE), hereditary pyropoikilocytosis (HPP), hereditary ovalocytosis [South Asian ovalocytosis (SAO)] and hereditary stomatocytosis (HSt) syndromes. These disorders are characterized by wide clinical and laboratory heterogeneity.

EPIDEMIOLOGY

Only the severe forms of patients of HS, HE, HPP, SAO, HSt come to the notice of physician or a hematologist (since most are asymptomatic) and hence the exact prevalence is not known. Nevertheless these conditions are seen with an increased frequency in Southeast Asia, Africa, and the Mediterranean. It is more common in malaria-endemic regions and presence of these conditions might confer some resistance against falciparum malaria.

Hereditary spherocytosis has an estimated prevalence ranging from 1:2,000 to 1:5,000. Approximately 75% of cases display an autosomal dominant pattern of inheritance, the remaining comprise of recessive forms and de novo mutations. During each pregnancy there are 50% chances that the child from either sex will be affected and 50% chances of being normal. Other way speaking one must always examine parents of a suspected child with HS.

Hereditary elliptocytosis, HPP, SAO, HSt mostly follow an autosomal dominant pattern of inheritance. The prevalence of HE in West Africa, for example, approaches 2%. HPP is known to occur more commonly in the African descent. The prevalence of SAO may be as high as 25% in several Southeast Asian ethnic groups.

These groups are primarily found in the Philippines, southern Thailand, Malaysia, Papua New Guinea, Indonesia, Borneo, Brunei, Cambodia, and in native Australians and certain native South Africans.

PATHOPHYSIOLOGY

The normal RBC membrane can be divided into two parts for the sake of understanding. The outermost part is a lipid bilayer in which complex proteins like palladin, glycophorin, etc. are embedded. The other part of the RBC membrane is composed of a helical cytoskeleton of α - and β -spectrin which is like a meshwork. Ankyrin attaches the lipid bilayer, band 3 (anion exchanger) and band 4.2 (palladin) to α - and β -spectrin helix while band 4.1 attaches glycophorin and the bilayer to the helix of α - and β -spectrin (**Fig. 1**). This structure provides RBC a biconcave shape and gives it the ability to traverse small and large blood vessels without undue damage. A qualitative or quantitative defect in any of these structural proteins, leads to weakening between the phospholipid bilayer and other proteins, making the RBC membrane rigid.

The RBC hydration is largely governed by the content of water and cations. To regulate the influx and efflux of Na^+ , K^+ , Ca^{2+} , and water across the membrane, a number of ion exchangers are present at the RBC membrane. A defect in any of these transporters will lead to a change in the RBC volume [mean corpuscular volume (MCV)] as well as its function. The common RBC membrane defects and their etiopathogenesis are described briefly:

Hereditary Spherocytosis

Ankyrin deficiency is the most common cause of HS. It could be inherited in an autosomal dominant or recessive manner. β -spectrin deficiency is also a common cause of autosomal dominant HS. α -spectrin deficiency causes autosomal recessive HS. Mutations affecting the production of the band 3 or 4.2 can also result in HS. The loss of these structural proteins leads to weak *vertical interactions* and/or decreased lipid anchoring. Membrane microvesicle formation occurs which causes loss of

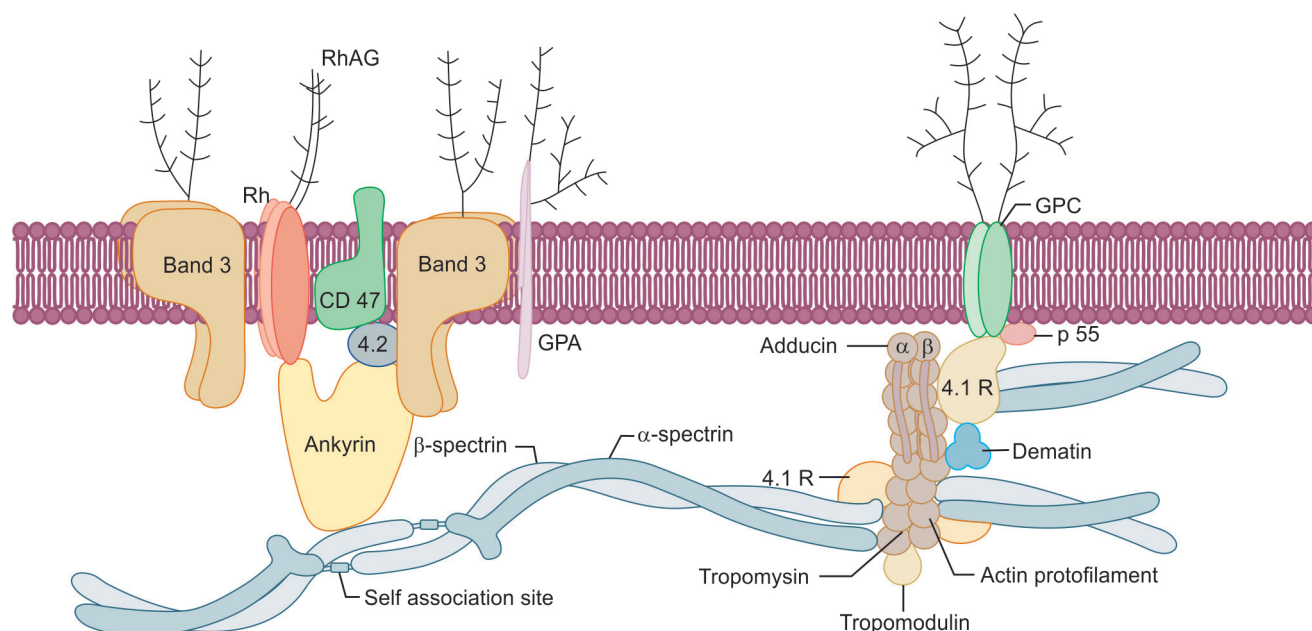


Figure 1 The lipid bilayer is seen embedded with complex proteins and the helical cytoskeleton of α - and β -spectrin is attached to the bilayer by ankyrin, palladin band 4.1

Abbreviations: GPC, glycophorin C; RhAG-Rhesus antigen

Source: Young NS, Gerson SL, High KA, eds. Clinical hematology. Mohandas N, Reid ME, Erythrocyte structure, pp 36-38. Copyright Mosby Elsevier; 2006. Reproduced with permission

surface to volume ratio. On continual loss of membrane, the RBC loses its biconcave shape and becomes a sphere. Spherocytes have increased permeability to sodium which is compensated by an increased work by a cation pump which leads to active transport of sodium out of the cell. This active transport is driven by glycolysis that generates the adenosine triphosphate needed by the cation pump. These rigid spherocytes, then undergo further membrane loss and ultimately hemolysis while traversing through the spleen resulting in a shortened RBC life span. Thus hemolysis is extravascular and spleen is the major site for hemolysis. This explains benefits of splenectomy in patients with most of the RBC membrane disorders.

Hereditary Elliptocytosis and Hereditary Pyropoikilocytosis

Hereditary elliptocytosis has an autosomal dominant inheritance. At the molecular level, abnormalities of α - and β -spectrin and defective spectrin heterodimer self-association lead to HE. These defects lead to alteration in *horizontal interactions* and result in gross membrane fragmentation. Less commonly, mutations in protein 4.1 and glycophorin C can produce elliptocytosis. Recently, HPP has been included as a subtype of homozygous HE, resulting from spectrin deficiency. The abnormal spectrin denatures at 45–46°C compared to the usual 49–50°C and hence the name. There is increased fragmentation of RBC membrane leading to presence of bizarrely shaped RBCs on smear.

South Asian Ovalocytosis

South Asian ovalocytosis generally occurs in the neonatal period. It is associated with an abnormal protein 3 which functions as an anion exchanger on the RBC membrane.

Hereditary Stomatocytosis

There are two variants of HSt, hydrocytic (overhydrated) and xerocytic (dehydrated). In the hydrocytic variant, which is more severe but less common, there is increase Na^+ influx into the cell. This leads to RBC imbibing more water intracellularly causing it to swell. Xerocytic HSt is more common and causes lesser anemia. In this condition there is a net loss of K^+ from the cell, resulting in eventual cellular dehydration.

CLINICAL FEATURES

There is a wide clinical heterogeneity in disorders of RBC membrane defects ranging from asymptomatic patients who are incidentally identified on peripheral smear examination done for unrelated conditions to severe hyperbilirubinemia requiring exchange transfusion in the neonatal period. Largely, these defects present with symptoms and signs related to hemolysis like anemia, jaundice (indirect hyperbilirubinemia) and pigmentary gallstones. Splenomegaly is generally a common finding on clinical examination. Those with severe anemia may develop hemolytic facies and increased diploic spaces in skull bones as evident on X-ray of skull bones. While most neonates with HS are asymptomatic, some may develop severe hyperbilirubinemia needing exchange transfusion. This is due to the presence of fetal hemoglobin (HbF). HbF binds poorly to 2,3-diphosphoglycerate (2,3-DPG). Consequently increased levels of 2,3-DPG destabilize spectrin-actin-protein 4.1 interactions in the red cell membranes, leading to hemolysis. Some of these babies will go on to develop anemia in first few months of life and typical spherocytes on peripheral smear examination.

Development of pigment gallstones is one of the most common complications of HS and it is related to the hepatic ability to metabolize the unconjugated bilirubin. A homozygous mutation

in the *UGT1A* gene in a case of HS increases the risk of developing gallstones at a younger age.

Like all hemolytic diseases, children with membrane defects (most commonly with HS) can also be affected by a number of potential *crisis*. The types of crisis that can occur are as follows:

- **Aplastic crisis** Generally caused by parvovirus B19, this can lead to sudden and severe anemia with reticulocytopenia and resultant cardiac failure. It can also lead to mild neutropenia and thrombocytopenia. A bone marrow examination at this time classically shows the presence of giant pronormoblast. It is a self-limited condition and generally only requires supportive care. In case the symptoms do not improve, one can give intravenous immunoglobulin (IVIG).
- **Megaloblastic crisis** Patients of hemolytic anemia have a higher daily requirement of folate. In situations of inadequate dietary intake, lack of supplementation or during recovery from the aplastic crisis, a relative folate deficiency may ensue, resulting in megaloblastic crisis. This can be easily prevented by administering folic acid 0.5–1 mg/day to all those with hemolytic anemias, irrespective of the cause.
- **Hemolytic crisis** During the episode of any viral syndrome, in a child less than 6 years with hemolytic anemia, a sudden increase in splenomegaly along with jaundice, anemia and reticulocytosis may be observed. These features are generally mild and do not require any active intervention.

Gout, chronic leg ulcers, spinocerebellar degeneration are some of the rare long-term complications seen in untreated patients.

DIFFERENTIAL DIAGNOSIS

A diagnosis of HS is very obvious in the face of recurrent anemia which may have needed transfusions but is not typically transfusion dependent, recurrent indirect hyperbilirubinemia, reticulocytosis, splenomegaly and a positive family history of similar anemia, indirect jaundice, blood transfusion, chronic leg ulcers or need for splenectomy in parents and siblings along with typical peripheral smear findings of microspherocytes and other evidence of hemolysis like macrocytes, polychromasia, basophilic stippling. During the neonatal period, ABO incompatibility is a close differential diagnosis of HS. ABO incompatibility, generally presents with anemia, spherocytes on smear with hyperbilirubinemia and splenomegaly. But a good clinical history, absence of a palpable spleen on examination of the parents, presence of ABO incompatibility setting and a positive Direct Coombs test will point towards ABO incompatibility.

Autoimmune hemolytic anemia (AIHA), may also present with anemia, jaundice, splenomegaly and spherocytes on peripheral smear. Nevertheless, a history of recent change in color of urine, acute onset of anemia and positive Coombs test, differentiates AIHA from HS.

APPROACH TO DIAGNOSIS

Like most hemolytic anemias, the classic laboratory features of RBC membrane defects comprise of mild to moderate anemia, reticulocytosis, indirect hyperbilirubinemia, a mild decrease in serum haptoglobin and increased lactate dehydrogenase (LDH) levels. Peripheral smear will show changes of hemolysis like macrocytosis, anisocytosis, basophilic stippling and polychromasia. Few specific features of the common types of membrane defects are as follows.

Hereditary spherocytosis The hemoglobin (Hb) will be normal to low with a high corrected reticulocyte count (3–15%). Mean corpuscular hemoglobin concentration (MCHC) greater than 36 g/dL is highly suggestive of HS. The peripheral smear will show the presence of microspherocytes, which are identified as small, darkly staining cells with absence of the normal central pallor (**Fig. 2**).

Hereditary elliptocytosis and hereditary pyropoikilocytosis In HE, peripheral smear will classically show presence of elliptocytes (15–50%). These cells are normochromic and normocytic. Spherocytes, ovalocytes, stomatocytes and fragmented cells may also be seen. In HPP, RBCs are of bizarre shapes and may show fragmentation and budding. This may reflect as a low MCV, owing to the presence of cell fragments (**Figs 3 and 4**).

Hereditary stomatocytosis More than 3–5% of stomatocytes [cells that have a mouth-shaped (stoma) area of central pallor] are classically seen in HSt. (**Fig. 5**). In the hydrocytic variant, a high MCV and decreased MCHC are observed. Peripheral smear shows the presence of stomatocytes. In the xerocytic variant, high MCV but with elevated MCHC is often diagnostic. On peripheral smear, target cells and echinocytes are seen, as well as dense erythrocytes that have Hb puddled at the periphery. Stomatocytes are usually not seen, and most RBCs have normal morphology.

Special Tests

Osmotic fragility test This is currently the most useful and sensitive laboratory test for diagnosing HS. Osmotic fragility (OF) measures the resistance of RBCs to hemolysis during osmotic stress. It is performed by exposing RBC to hypotonic solutions of varying tonicity (from 0.9% to 0.1%). The test is read colorimetrically at the end of 30 min. Incubating RBC at 37°C for 24 hours, improves the sensitivity of the test. Normally hemolysis begins with 0.5% solution and complete hemolysis is seen with 0.2–0.3% solution. In HS, the hemolysis starts at 0.7% and complete hemolysis is seen at 0.4–0.5%. In HE also, OF is increased but not as much as in HS. The OF in a case of HS or HE may be falsely normal if there is superadded iron, folate or vitamin B₁₂ deficiency, β -thalassemia or Hb SC disease.

Acidified glycerol lysis test and pink test These are modifications of the OF test and are based on the same principle. Since this test is faster and more sensitive, it is now used as a rapid screening test to diagnose HS.

Hypertonic cryohemolysis test The principle of this test is based on the fact that HS cells are sensitive to cooling at 0°C in hypertonic solutions. It is claimed that this test is 90–100% sensitive, 94% specific for HS and 86% specific for cases of AIHA. But this test is rarely used in clinical practice.

Autohemolysis test After 48 hours of incubation of normal RBC, without glucose, less than 5% autohemolysis. In HS and other membrane defects, autohemolysis increases to 15–45%. If glucose is added during the incubation, hemolysis in HS is reduced whereas in RBC glycolytic disorder, the autohemolysis is not reduced.

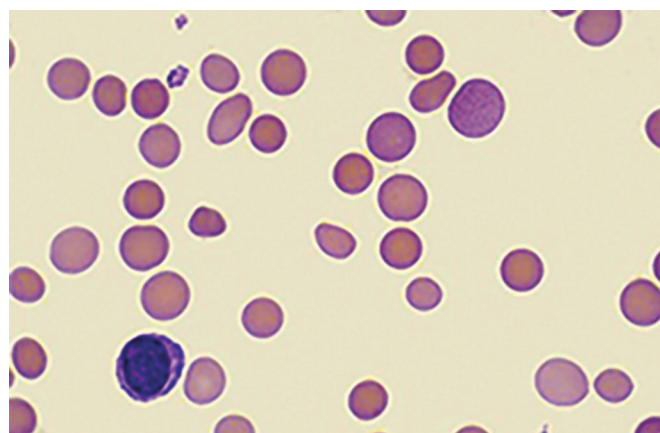


Figure 2 Peripheral smear of hereditary spherocytosis: densely hemoglobinized spherocytes are seen

Ektacytometry This method is used to assess the surface-to-volume ratio and RBC membrane strength. Although few studies have observed 100% specificity of this test, compared with 66% rate of detection by the OF test in cases of HS, it is available in very few research laboratories.

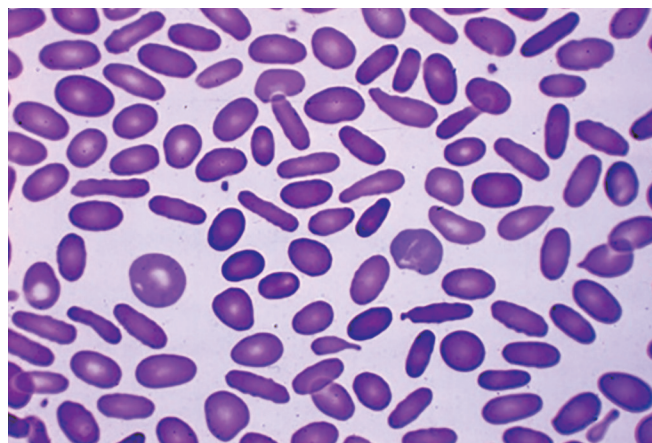


Figure 3 Peripheral smear of hereditary elliptocytosis: pencil shaped elliptocytes are seen

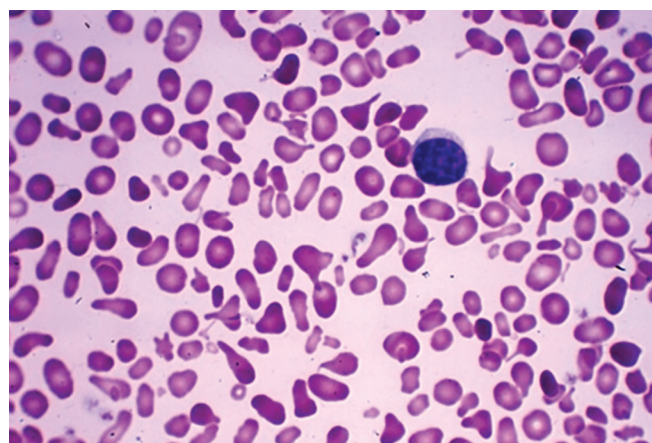


Figure 4 Peripheral smear of hereditary pyropoikilocytosis: multiple fragmented cells with bizarre shapes are seen

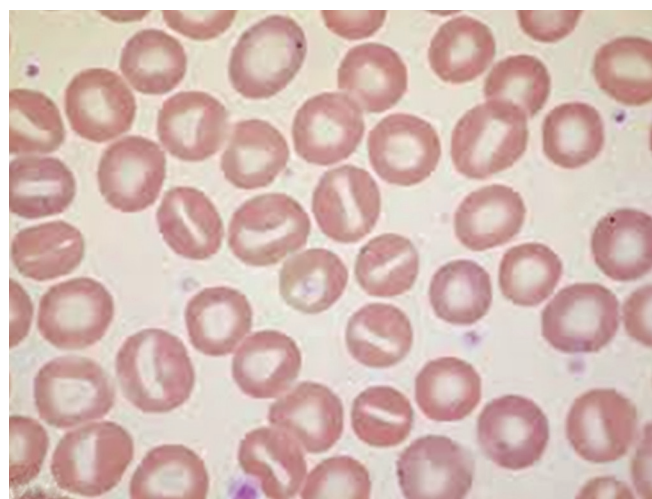


Figure 5 Peripheral smear of hereditary stomatocytosis: multiple cells with 'stoma' shaped central pallor are seen

Quantifying membrane proteins, RNA or DNA Generally these specialized tests are done for confirmation. Membrane proteins are usually assessed with sodium dodecyl sulfate polyacrylamide (SDS-PAGE) gel electrophoresis. SDS gel electrophoresis is used to identify spectrin, ankyrin, protein 4.2 and band 3 deficiencies.

Also, suspected proteins or genomic DNA can be sequenced by PCR technique. But in the clinical setting these are not frequently used.

MANAGEMENT

Packed Red Blood Cell Transfusion

Most patients with membranopathy do not have severe anemia and do not need regular transfusions unlike a child with thalassemia major. In fact unnecessary and haphazard transfusions will lead to iron overload. Many patients can tolerate Hb as low as 6–7 g%. Indications for transfusions include presence of pedal edema, exercise intolerance, impending or overt cardiac failure, and severe growth retardation. In presence of infections, fever, cardiac illness or respiratory illness one may transfuse at higher Hb levels of 7–8 g% to tide over the crisis temporarily. Those who are transfused should be followed up regularly with Hb levels, growth monitoring to ascertain need for transfusion and development of complications. Abdominal sonography should be done every 2–3 years from 5 years of age to assess the development of gallstones. Iron studies should be done annually to look for iron overload and chelation should be started when ferritin rises to more than 500–1,000 ng/mL.

Folate Administration

There is an erythroid hyperplasia in the bone marrow in cases of RBC membrane defects. In view of this increased cellular production in the marrow, a relative folate deficiency can ensue especially in cases of inadequate dietary intake, periods of growth spurts, etc. Hence, folate must be administered to all patients of membrane defects at a dose of 0.5–1 mg/day to prevent megaloblastic crisis (see above).

Splenectomy

Since all inherited RBC membrane defects exhibit extravascular hemolysis and the predominant site of hemolysis is the spleen, splenectomy is the logical treatment option in most cases where there is significant anemia, except for hereditary xerocytosis in which case it is an absolute contraindication. A rough cut-off for splenectomy in cases of membrane defects, is a persistent Hb level of lower than 7 g%, reticulocyte count of more than 10% and severe growth failure. One can also consider splenectomy when cholecystectomy is contemplated for symptomatic gallstones. In most cases, the Hb normalizes, reticulocyte count decreases (1–3%) and RBC life span improves to almost near normal. The clinical improvement is also striking. But the benefits of splenectomy must be carefully weighed against the risks of overwhelming postsplenectomy sepsis.

Complications of Splenectomy

Overwhelming Postsplenectomy Infection (OPSI)

The spleen has an important immunological function against encapsulated bacteria viz. *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Neisseria meningitidis*. The splenic macrophages phagocytose the opsonized encapsulated bacteria and cause its removal from the body. In the absence of spleen these bacteria proliferate and can cause fulminant sepsis and a high mortality. A way to prevent this complication is to immunize children against these organisms at least 6–8 weeks prior to splenectomy. As the risk of sepsis with these encapsulated organisms is maximum in the first 3–5 years of life, if feasible, splenectomy must be delayed until 5–9 years of age and should almost never be performed in a

child less than 3 years of age, even if recurrent blood transfusions are required in the interim. Postsplenectomy penicillin prophylaxis is given to the patients with oral penicillin V in the dose of 200 mg twice a day for children less than 30 kg and 400 mg twice a day for those more than 30 kg weight and this is continued lifelong. They are also instructed to double the dose of oral penicillin when they develop fever and seek appropriate medical help as soon as possible. Combined approach with immunization, penicillin prophylaxis and timely management of febrile episodes has significantly brought down the incidence and mortality of postsplenectomy sepsis. Of note, splenectomised individuals are also susceptible to *Capnocytophaga canimorsus*, malaria and babesiosis.

Thrombocytosis

Spleen filters almost 10–15% of the blood volume per minute. It filters the platelets in particular, a mechanism called *culling*. Hence, postsplenectomy thrombocytosis is frequently observed. But this alone, needs no treatment.

Thrombosis and Thromboembolism

There is an increased prevalence of thrombosis postsplenectomy. The etiology of thrombosis is complex. Chronic postsplenectomy thrombocytosis with platelet aggregation, decreased nitric oxide (NO) affecting vascular tone (postsplenectomy there is increased free circulating Hb which binds to NO), stasis, etc. are few of the postulated mechanisms. Thromboembolic episodes are treated with heparin and warfarin as per standard guidelines.

OUTCOME

Anemia, acholuric jaundice, splenomegaly and gallstones constitute the clinical spectrum of most membranopathies in children. Once diagnosed on the basis of complete blood count (CBC), peripheral smear and confirmatory tests, these children must be followed up regularly for evaluation of growth, transfusion dependency and surveillance of complications.

IN A NUTSHELL

1. RBC membrane defects are an important cause of hemolytic anemia in children. Most are asymptomatic and have a wide clinical spectrum of presentation.
2. The most common mode of inheritance is autosomal dominant.
3. The hemolysis in RBC membrane defects is mostly extravascular and occurs in the spleen.
4. Anemia, indirect hyperbilirubinemia, splenomegaly and cholelithiasis are the most common findings.
5. Folic acid administration (2.5–5 mg/day) is mandatory for all patients.
6. Splenectomy causes marked clinical improvement in most membrane defects but is contraindicated in hereditary xerocytosis.

MORE ON THIS TOPIC

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Chapter 38.13

Red Blood Cell Enzyme Defects

Manoranjan Mahapatra

Mature red blood cells (RBCs) are unable to carry out oxidative phosphorylation and protein synthesis due to the loss of the nucleus, mitochondria, and ribosomes. However, it is optimally adapted to perform its most important function, i.e., the binding, transport and delivery of oxygen to all tissues. Red cell enzymes allow erythrocytes to meet these tasks by supporting three essential metabolic pathways:

- *Antioxidant pathways* necessary for the protection of RBC proteins against oxidation, through the synthesis of glutathione (GSH), and of hemoglobin against iron oxidation through the maintenance of iron in its functional, reduced, ferrous state (cytochrome b5 reductase).
- *Anaerobic glycolysis*, which is the only source of energy (ATP production) for maintenance of cell structure and function.
- *Nucleotide metabolism* for the maintenance of the purine and pyrimidine nucleotides.

Erythrocytes possess a unique glycolytic bypass for the production of 2,3-bisphosphoglycerate (2,3-BPG) a crucial metabolite in the regulation of hemoglobin affinity for oxygen. RBC enzyme defects have been described in all these metabolic pathways and almost all are associated with chronic hemolytic anemia (CHA), with the exception of the enzymopathies of the pentose phosphate pathway and glutathione metabolism, which are associated with acute hemolytic crises only after exposure to oxidant substances. In general, the genetic mutations that cause RBC enzyme defects are associated with three different clinical phenotypes:

1. Hemolytic syndrome associated with either CHA, hereditary nonspherocytic hemolytic anemia (HNSHA) or acute hemolytic crises (**Box 1**)
2. Permanent cyanosis with methemoglobinemia and
3. Increased RBC mass or erythrocytosis.

Over the past few years the inherited disorders of erythrocyte metabolism have been the object of intensive research which has resulted in a better understanding of their molecular basis. However, curative therapy for RBC enzyme defects still remains challenge.

BOX 1 RBC enzyme deficiencies associated with hemolytic anemia

- Hexose monophosphate (HMP) pathway deficiency
 - Glucose-6-phosphate dehydrogenase (G6PD)
 - Others
 - Glutathione reductase
 - Glutathione synthetase
 - Gamma-glutamylcysteine synthetase
- Embden–Meyerhof (EM) pathway deficiency
 - Pyruvate kinase (PK)
 - Others (rare, only small case series reported)
 - Glucose phosphate isomerase
 - Hexokinase
 - Phosphofructokinase
 - Triose phosphate isomerase
 - Phosphoglycerate kinase
 - Aldolase
- Abnormalities of nucleotide metabolism
 - Pyrimidine 5' nucleotidase (P5'N-1) deficiency
 - Adenylate kinase deficiency.

GLUCOSE-6-PHOSPHATE DEHYDROGENASE (G6PD) DEFICIENCY**Biology**

Glucose-6-phosphate dehydrogenase is a house keeping enzyme essential for basic cellular functions, including protecting red cell proteins from oxidative damage. G6PD catalyzes the first step in the hexose monophosphate shunt which is necessary for producing nicotinamide-adenine dinucleotide phosphate (NADPH). The enzymatic activity of G6PD generates NADPH that is utilized for glutathione reduction. Reduced glutathione restores hemoglobin to the soluble form. Thus, maintaining a high ratio of reduced-to-oxidized glutathione represents the major defense against oxidative damage of hemoglobin. Reticulocytes have five times higher G6PD enzyme activity than the oldest erythrocyte subpopulation.

Epidemiology and Clinical Phenotypes

Glucose-6-phosphate dehydrogenase deficiency is the most common known enzymopathy and it is estimated to affect 400 million people worldwide. Drug-induced hemolytic anemia due to G6PD deficiency has a high frequency in some populations, for example, Mediterranean's such as Sardinians 30%; south-east Asians especially Indians, Chinese, Malays, Thais, Filipinos, Melanesians; and blacks.

There is evidence to suggest that the defect confers some protection against falciparum malaria; thus it may decrease the severity of malarial infections in young children and infants. However, the mechanism of protection is unknown. Early studies of females heterozygous for G6PD deficiency showed higher levels of malaria parasites in normal compared to G6PD deficient red cells. Although malaria invasion of the cells was similar, the growth of the parasites in the G6PD deficient cells was inhibited. Similarly, conflicting results have been reported about whether hemizygous G6PD deficient males have protection against malaria. The most likely mechanism of malarial protection may be increased phagocytosis of G6PD deficient erythrocytes containing the early ring-stage parasites. In the ring-stage parasite-infected cells, the level of reduced glutathione was lower in the G6PD deficient cells compared with normal red cells, leading to membrane damage of deficient cells containing parasites that may be preferentially targeted for destruction.

G6PD deficiency is X-linked and caused by different mutations in the G6PD gene, resulting in protein variants with different levels of enzyme activity that are associated with a wide range of biochemical and clinical phenotypes. G6PD variants can be divided into three categories based on the type of hemolysis. Most common are those variants associated with acute intermittent hemolytic anemia; some of these variants are endemic. In contrast, the variants associated with CHA are very rare and the severity of hemolysis is highly variable, ranging from mild to transfusion dependent. The third type of variant is associated with no obvious risk of hemolysis. In 1967, an expert committee of the WHO proposed standard biochemical procedures for characterizing variants, such as enzyme activity, heat stability and electrophoretic pattern. After this, the WHO introduced a classification of G6PD variants into five classes according to the severity of the clinical phenotype. Class I: severe enzyme deficiency with chronic nonspherocytic hemolytic anemia; Class II: severe enzyme deficiency (less than 10% of normal); Class III: moderate-to-mild enzyme deficiency (10–60% of normal); Class IV: mild or no enzyme deficiency (60–100% of normal); and Class V: increased enzyme activity more than twice normal.

There appeared to be two types of mutations among Africans: G6PD A, a normally active enzyme with rapid electrophoretic mobility, and G6PD A⁻, an enzyme with the same mobility as G6PD A, but with diminished activity. Drug-induced hemolytic anemia in Greeks and Italians is usually due to the presence of G6PD Mediterranean. The deficiency of this enzyme is more severe

than that of the A⁺ type found in Africans, and this is reflected in susceptibility to a wider range of drugs. Affected patients may also develop neonatal jaundice and acute hemolysis on exposure to fava beans, both of which are rarely seen in Africans.

Clinical Features

Acute Hemolysis

The clinical features are those of an acute hemolytic anemia. In a subject with an acute intermittent hemolytic G6PD deficient variant, there is no clinical or laboratory evidence of hemolysis unless the individual is exposed to oxidants (drugs), infections or fava beans. The most common offending agents are drugs (**Box 2**). The severity of the hemolytic episode induced by a particular drug is, in general, related to its dose. This results in a self-limiting hemolysis, commencing in 2–3 days, and lasting for approximately 7 days, and followed by a return of the hemoglobin value to normal after 20–30 days despite continued drug administration. The self-limiting nature of the hemolysis is because RBC drug sensitivity is a function of cell age; older cells are destroyed, while younger cells are resistant. In some nonblack patients, the hemolysis is not self-limiting; in such patients withdrawal of the drug is of great importance.

Favism

Ingesting fava beans has been known since antiquity to induce hemolytic anemia in some individuals. It is characterized by acute hemolytic anemia of sudden onset, often with hemoglobinuria and mild jaundice, which occurs in persons sensitive to the fava bean, *Vicia fava*. More common in children, cases of hemolysis in breastfed infants of mothers who have ingested fava beans have been described. The degree of hemolysis varies in severity, but the anemia is usually severe; attacks last for 2–6 days, followed by spontaneous recovery, but death has been reported. Although favism occurs typically in Mediterranean people carrying the severe Mediterranean type of G6PD deficiency, it may also occur in certain non-Mediterranean persons with G6PD deficiency, including Chinese and Jews. All patients with favism are G6PD deficient, but many G6PD deficient individuals can eat fava beans with impunity. Thus, the deficiency is a necessary but not sufficient cause of hemolysis.

BOX 2 Common drugs that cause hemolysis in patients with G6PD deficiency

- *Analgesics*
 - Acetanilide
- *Antibiotics*
 - Nitrofurantoin
 - Nitrofurans
- *Antimalarial*
 - Primaquine
- *Sulfonamides*
 - Sulfacetamide
 - Sulfamethoxazole
 - Sulfanilamide
 - Sulfapyridine
 - Sulfasalazine
- *Others*
 - Methylene blue
 - Naphthalene
 - Phenylhydrazine
 - Toluidine blue
 - Phenazopyridine
 - Isobutyl nitrate.

Nonspherocytic Congenital Hemolytic Anemia

Another manifestation of G6PD deficiency was found to be hereditary nonspherocytic hemolytic anemia. They differ in severity and in hematological features, but as a group have in common the fact that spherocytes are not present on the blood film, the osmotic fragility of fresh blood is not usually increased, and splenectomy usually gives little or only moderate benefit. Most cases are due to an enzyme deficiency, although occasional cases are due to unstable hemoglobins.

Neonatal Jaundice

Glucose-6-phosphate dehydrogenase deficiency has an association with neonatal jaundice and, rarely, kernicterus in Mediterranean and Chinese infants. The jaundice is sometimes accentuated by exposure to vitamin K derivatives or other inciting drugs. Affected infants are usually mildly anemic. Quite understandably, it is commonly believed that this is a consequence of hemolysis, but in reality the hemoglobin level and reticulocyte count of the infants are generally normal, and using modern techniques it is been shown that there is only a modest and inconsistent shortening of red cell life span, which may contribute to a limited extent to the jaundice. The principal cause of neonatal icterus in G6PD-deficient infants is the inability of the liver to adequately conjugate bilirubin.

Investigations

The possibility of drug-induced hemolysis due to G6PD deficiency or favism should be considered in any patient with an unexplained acute hemolytic anemia in which the antiglobulin (Coombs) test is negative. When the diagnosis is suspected on clinical grounds, a screening test should be performed and, if possible, an enzyme assay.

Screening Tests

For diagnosis of G6PD deficiency, several screening tests are available. The principle of the test to demonstrate the presence or absence of G6PD by testing the ability of the RBCs to generate NADPH from NADP, a reaction that directly depends on the availability of G6PD.

Brilliant cresyl blue dye test NADPH reduces brilliant cresyl blue (BCB) to a colorless compound.

Methemoglobin reduction test Nitrite is used to oxidize hemoglobin to methemoglobin. Methylene blue stimulates the hexose monophosphate pathway, which if intact, supplies NADPH, which in turn reduces brown methemoglobin to red oxyhemoglobin.

Fluorescent spot test Nicotinamide-adenine dinucleotide phosphate fluoresces when activated by long-wave ultraviolet light. The screening tests satisfactorily detect hemizygous males and homozygous females.

Enzyme Assay

The enzymatic activity of G6PD can be assessed by quantitative spectrophotometric analysis. However, false-negative results are possible in milder forms of G6PD deficiency, especially if enzymatic analysis is performed shortly after resolution of acute hemolytic episodes when young erythrocytes, which have much higher enzymatic activity, predominate. The assay should be repeated 2–4 months after the hemolytic episode in patients in whom the diagnosis of G6PD deficiency is definitely suspected, despite a normal G6PD activity on assay during or shortly after hemolysis. Females heterozygous for G6PD deficiency are particularly difficult to diagnose by enzymatic assays, but now that the nucleotide substitutions of many G6PD deficient isoenzymes

have been established, molecular diagnostic methods can be used for the diagnosis of females who are heterozygous for common variants.

Therapy

Drugs that are known to precipitate hemolysis in G6PD deficient subjects should be avoided. In subjects with G6PDA⁻ deficiency, hemolysis is typically short lasting in spite of continuous use of the offending agent. This is not always the case in the more severe Mediterranean variant of G6PD deficiency, and the precipitating agent should always be withdrawn. When anemia is severe and symptomatic, blood transfusion may be necessary. Folate supplementation should be provided in those patients with chronic hemolysis.

PYRUVATE KINASE DEFICIENCY

Molecular Biology

The molecular biology of pyruvate kinase (PK) is complex. PK catalyzes the irreversible transfer of a phosphoryl group from phosphoenolpyruvate (PEP) to ADP, thus yielding pyruvate and ATP; it is a regulatory key enzyme of the glycolytic pathway. Four different PK isoenzymes (PK-M1, PK-M2, PK-L, and PK-R) are generated by the use of alternative promoters of two distinct genes (*PKLR* and *PKM*) that have variable expression in different tissues. The R isoform is unique to erythrocytes and gradually replaces the M2 isoform found in early erythroid and myeloid progenitors.

Clinical Presentation

Pyruvate kinase deficiency is the most common enzymopathy associated with CHA, and about 300 patients have been reported so far. The clinical severity of this disorder varies widely, ranging from a mildly compensated anemia to severe anemia of childhood. Affected individuals are either homozygous for the same mutation or compound heterozygotes for two different PK defects. PK deficiency is distributed worldwide, but it has been reported that the gene is more common among people of northern European extraction and perhaps Chinese and certain other ethnic and racial groups. Patients with severe hemolysis may be chronically jaundiced and may develop the clinical complications of chronic hemolytic states, including gallstones, transient aplastic anemia crises (often due to parvovirus infection), folate deficiency, and, infrequently, skin ulcers. In general, the clinical and hematological features tend to remain fairly constant in the individual patient, but there may be variation in severity in the same family; intercurrent infection, pregnancy, or surgery may cause a temporary increase in anemia.

Diagnosis

The diagnosis should be considered in any case of nonspherocytic congenital hemolytic anemia, especially when the clinical features suggest autosomal recessive inheritance. There are no specific clinical findings or morphological abnormalities in PK deficiency and no routinely available laboratory measurements aid in diagnosis. A fluorescent screening test for the diagnosis of PK deficiency is available. Specialized laboratories can perform quantitative PK enzyme analysis. Due to the large number of the mutations and their low prevalence, it is difficult to replace these tests with molecular diagnostic methods. There is often poor correlation between the enzyme level and the severity of the hemolytic anemia. Prenatal enzymatic testing is not optimal, because a large amount of fetal blood is required, and the test has a high rate of false-negative results.

Treatment

Treatment is supportive and includes folic acid supplementation in patients with mild and moderate PK deficiency. RBC transfusions may be necessary if the hemoglobin level decreases significantly, during infections, or during stress such as pregnancy or surgery. Splenectomy is indicated only for patients with severe anemia. Large doses of salicylates should be avoided in patients with severe anemia, because salicylates inhibit oxidative phosphorylation, thereby causing further ATP depletion.

GLUCOSE PHOSPHATE ISOMERASE DEFICIENCY

Glucose phosphate isomerase deficiency is the second most common erythroenzymopathy of glycolytic enzymes after PK deficiency, and approximately 50 different cases have been described to date. It is an autosomal recessive genetic disorder associated with mild to severe CHA in homozygotes or compound heterozygotes. In a very few cases, GPI deficiency is associated with neurological impairment and granulocyte dysfunction.

PYRIMIDINE 5'-NUCLEOTIDASE (P5'N-1) DEFICIENCY

Pyrimidine 5'-nucleotidase deficiency is an autosomal recessive disorder characterized by CHA with marked reticulocytosis and increased concentrations of pyrimidine nucleotides within mature erythrocytes, a characteristic RBC morphological abnormality is a heavy basophilic stippling, and its observation is very helpful for P5'N diagnosis. P5'N-1 deficiency can also be acquired as a result of lead poisoning or oxidative stress. Lead is a powerful inhibitor of P5'N and determination of lead levels should be included whenever the constellation of hemolytic anemia, P5'N deficiency, and basophilic stippling is found. Lead-induced acquired P5'N deficiency is treatable, unlike the congenital deficiency for which no therapy is available.

RBC ENZYMOPATHIES ASSOCIATED WITH METHEMOGLOBINEMIA

Methemoglobin is the derivative of hemoglobin in which the iron of the heme group is oxidized from the ferrous (Fe²⁺) to the ferric (Fe³⁺) state. The ferric hemes of methemoglobin are unable to bind oxygen and, in addition, the oxygen affinity of the accompanying ferrous hemes in the hemoglobin tetramer is increased. As a result, the oxygen dissociation curve is left shifted and oxygen delivery is impaired. Methemoglobinemia is usually a result of either enhanced methemoglobin production or decreased methemoglobin reduction. The primary reaction that reduces methemoglobin back to hemoglobin is catalyzed by the reduced form of nicotinamide-adenine dinucleotide (NADH)-cytochrome b5 reductase (b5R).

Methemoglobinemia due to b5R deficiency can be classified into two main groups with drastically different clinical manifestations. In one group, patients not unwell and the only clinical manifestation is cyanosis (hereditary b5R deficiency type I), which can be treated with the administration of methylene blue. In the other group, in addition to cyanosis there is a much more severe clinical syndrome characterized by microcephaly, opisthotonus, retarded growth and progressive neurological impairment leading to generalized hypertonía, mental retardation and death before puberty (hereditary b5R deficiency type II).

RBC ENZYMOPATHIES ASSOCIATED WITH ERYTHROCYTOSIS

Congenital erythrocytosis can result from an extremely rare RBC enzymopathy due to bisphosphoglycerate mutase (BPGM) deficiency. Only two affected families have been described so far. In both cases patients had a complete deficiency of erythrocyte BPGM, increased ATP levels, ruddy cyanosis, high hemoglobin concentration and no evidence of hemolysis.

MORE ON THIS TOPIC

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IN A NUTSHELL

1. RBC enzyme defects are associated with three different clinical phenotypes: (i) Hemolytic syndrome associated with either chronic hemolytic anemia (CHA) or acute hemolytic crises; (ii) permanent cyanosis with methemoglobinemia and (iii) increased RBC mass or erythrocytosis.
2. Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common enzymopathy associated with hemolytic anemia. However, patients with a longstanding CHA, one should suspect either PK deficiency or another glycolytic enzymopathy, or unstable hemoglobin.
3. In G6PD deficient individual, hemolysis usually occurs when the subject is exposed to oxidants, infections or fava beans. The most common offending agents are drugs.
4. For diagnosis of G6PD deficiency, several screening tests are available. Commonly used screening tests are brilliant cresyl blue (BCB) dye test, methemoglobin reduction test and fluorescent spot test. The enzymatic activity of G6PD can be assessed by quantitative spectrophotometric analysis.
5. Pyruvate kinase and glucose phosphate isomerase (GPI) are two other common RBC enzymes whose deficiencies result in CHA.

Chapter 38.14

Immune Hemolytic Anemia

Nita Radhakrishnan, Anupam Sachdeva

Autoimmune hemolytic anemia (AIHA) is characterized by production of antibodies directed against red blood cells (RBCs) and destruction by the mononuclear phagocytic system or complement system. Alloimmune hemolytic anemia on the other hand, occurs following exposure to red cells as in prior blood transfusion, pregnancy and transplantation. Advances in the pathogenesis and diagnostic modalities have led to refinement in the treatment of this disorder. AIHA is the most common cause of extracorporeal hemolysis in pediatric age group. AIHA observed in children is usually self-limiting and often precipitated by a viral infection. However, in adults the disease is usually secondary to autoimmune diseases, malignancy or infection, and often runs a prolonged course. Identifying the underlying disorder is very important considering the serious nature of it. Treatment aimed at specific targets in the immune system has emerged over the last decade for AIHA.

ETIOPATHOGENESIS AND APPROACH TO DIAGNOSIS

Autoimmune hemolytic anemia may also be classified into primary or secondary based on the etiology of the autoantibody. In primary AIHA there is no finding other than hemolytic anemia. Primary AIHA is further classified on the basis of the temperature at which the pathogenic antibody reacts with RBCs into warm, cold and mixed types. In secondary, an underlying cause of RBC autoantibodies can be identified (**Table 1**). Accurate diagnosis is essential for assessing the clinical features and for deciding and titrating management. The basic cause of autoantibody production is the failure of the immune system to recognize *self*. This occurs due to the failure of T-cell regulation of B-cells or due to subtle alterations in the antigenic structure of the patient's red cells. Inflammatory disorders, drugs, lymphoproliferative conditions, infections and genetic factors also contribute to initiating autoantibodies. In more than 80% of the patients, the destruction of the red cells is extravascular due to interaction of red cells coated with antibody or complement or both, interacting with

Table 1 Classification of autoimmune hemolytic anemia (AIHA)

I. Warm reactive AIHA
1. Primary/Idiopathic
2. Secondary
• Lymphoproliferative disorders
• SLE and other chronic inflammatory disorders
• Nonlymphoid malignancies
• Drug-induced AIHA
II. Cold reactive AIHA
A. Cold agglutinin syndrome
• Primary/Idiopathic
• Secondary
– Postinfectious (IMN/Mycoplasma)
– B-cell lymphoproliferative disorder
B. Paroxysmal cold hemoglobinuria
III. Mixed type AIHA
Primary/Idiopathic
Secondary: seen in rheumatic disorders
IV. Drug-induced AIHA

mononuclear phagocytes. In the rest intravascular destruction occurs due to the interaction of red cells with lymphoid cells or granulocytes. Fixation of complement on the RBC surface leads to clearance by the reticuloendothelial system or amplification of complement cascade and formation of pores on the cell surface membrane. Serological specificity of the antibody is also clinically significant. Pan reactive autoantibody suggests that the antibody reacts to a surface antigen that is common to all human RBCs. Rh protein is the main antigenic determinant in warm reactive antibodies. IgM antibodies react against the polysaccharides on the RBC surface like I/i antigen rather than surface antigens.

Warm Autoimmune Hemolytic Anemia

Warm reactive antibodies are commonly seen in children especially in the age group 2–12 years and accounts of more than 60% of the cases. Although it is idiopathic in around half of the cases, secondary causes include infections, drug induced and autoimmune causes. Immunoglobulin G (IgG) is the class of autoantibody observed and it has maximal reactivity at 37°C. Warm AIHA may also be observed with IgA and IgM. RBCs bound to the autoantibodies, are removed in the spleen after binding to the Fc receptors within the spleen.

Cold Reactive Autoimmune Hemolytic Anemia

Cold reactive autoantibodies cause two distinct classes of AIHA; paroxysmal cold hemoglobinuria (PCH) and cold agglutinin syndrome (CAS).

Paroxysmal Cold Hemoglobinuria

Paroxysmal cold hemoglobinuria is otherwise called Donath-Landsteiner syndrome because the antibody in question is a polyclonal IgG antibody, which is a biphasic hemolysin. It activates complement at cold temperature by bringing the P antigen on the RBC. Intravascular hemolysis occurs in body temperature subsequently. PCH is commonly observed in children usually after a bout of viral respiratory illness. Previously, syphilis was identified as an etiology, but this is becoming less and less common. Infections such as mycoplasma, Epstein-Barr virus (EBV), varicella, hepatitis, mumps, cytomegalovirus (CMV), parvovirus and rubella may be ruled out.

Cold Agglutinin Syndrome

In children, CAS is much less common than warm AIHA or PCH. It occurs usually in the middle aged and elderly with a peak incidence at around 70 years of age. In CAS, hemolysis is caused primarily by C3 proteins, which lead to autoantibody-dependent lysis. Red cell phagocytosis also occurs in the liver. In CAS patients exhibit variable tendency to hemolysis and hence need for transfusions differ. The degree of hemolysis is dependent on active autoantibody concentration rather than abundant membrane bound C3 protein concentration. In CAS, the IgM antibodies bind to RBCs under cold conditions and cause their agglutination. They also initiate binding of complement to the RBC surface. The complement initiates hemolysis, which is mainly intravascular in nature. Infections and lymphoproliferative conditions are the usual secondary causes for CAS in adults. In children and young adults infectious etiology such as mycoplasma infection or infectious mononucleosis should be ruled out.

Mixed Type Autoimmune Hemolytic Anemia

Mixed type AIHA is characterized by both warm and cold antibodies that react with different RBC antigens. They account for a minor percentage of the total AIHA cases and is seen usually secondary to drugs and rheumatological conditions.

Secondary Autoimmune Hemolytic Anemia

In conditions where the reason for autoantibodies against red cells in another underlying disease, and hemolytic anemia is just one of the manifestations of this systemic illness, secondary AIHA may be considered. It is seen in patients with systemic lupus erythematosus (SLE) and other autoimmune inflammatory conditions. It also occurs in children with immunodeficiency such as common variable immunodeficiency (CVID), specific infections, certain drugs, etc. Evans syndrome is a clinical entity, which is associated with autoimmune pancytopenia although commonly red cells and platelets are most affected. Also, in children with persistent symptoms, autoimmune lymphoproliferative syndrome (ALPS) may be considered.

Drug-induced Autoimmune Hemolytic Anemia

Drug-induced AIHA is relatively rare and may go undiagnosed for a long time. Drug-induced AIHA is classified as drug dependent and drug independent AIHA, drug dependent AIHA occurs mainly due to two mechanisms: (1) Drugs such as penicillins, cephalosporins, etc., act as haptens and bind to the RBC. This drug-RBC complex is targeted by the autoantibody that results in lysis. (2) Drug autoantibody immune complexes are mediated by a complement dependent hemolysis.

Drug-dependent antibodies induce a response only when the drug is present. The antibody attaches to the drug, the drug's metabolites or the drug-RBC complex. The RBC lysis occurs via Fc receptor mediated mechanisms similar to warm AIHA. Hapten and drug adsorption mechanisms have been implicated with penicillin, cephalosporin, tetracycline, etc., whereas immune or ternary complex mechanism has been observed with cephalosporins, amphotericin B, rifampicin, probenecid, and diclofenac. Drug-independent antibodies are capable of causing an immune response even in the absence of the offending drug. Drugs such as methyldopa, cladribine and fludarabine stimulate autoantibody production, which results in RBC lysis. For treatment, discontinuation of the offending drug and supportive transfusions is usually enough. Most drugs are cleared rapidly from the body whereas the membrane bound antibodies may persist. Drugs implicated in AIHA and its pathogenic mechanisms have been detailed in **Table 2**.

CLINICAL MANIFESTATIONS

Anemia and jaundice are usual initial manifestations. Symptoms of anemia include tiredness, fatigue, dizziness and effort intolerance. The onset of symptoms is usually slow and insidious. However, especially in children the onset may be abrupt and often life-threatening. In children with PCH the presenting symptoms are abdominal pain, fever and dark colored urine that indicate

intravascular hemolysis. Exacerbation of pallor and hemolysis with hemoglobinuria is observed in cold environment with cold reactive antibody. On clinical examinations, patients with rapid onset of the disease may exhibit tachycardia and features of cardiac failure. However, unlike patients with acute onset of hemolysis such as in G6PD deficiency or malaria, anemia is usually well compensated. Splenomegaly is seen in 20% of the patients. In patients with CAS, acrocyanosis and vaso-occlusive phenomenon affecting ears, nose and fingers may be observed. In secondary AIHA, the features of the underlying disease should be looked. Lymphadenopathy, splenomegaly and hepatomegaly suggest an underlying infection, malignancy or inflammatory disorder. Children with AIHA have unremarkable past medical history and family history. History pertaining to SLE and other autoimmune inflammatory conditions must be considered and appropriate investigation should be undertaken to exclude these disorders if required.

DIAGNOSIS

Hemoglobin is usually in the range of 4-7 g% and red cell indices may be apparently normal. Microspherocytes along with large reticulocytes may falsely normalize mean corpuscular volume (MCV). In patients with cold agglutinin disease and red cell agglutination, falsely elevated MCV may be noticed. MCHC may be elevated due to the presence of spherocytes. Low platelet count should warrant a search for bone marrow failure syndromes, bone marrow infiltration, microangiopathy or Evans syndrome. Neutropenia or pancytopenia also needs further work-up for bone marrow pathology or autoimmune causes. Peripheral smear is vital in evaluating children with suspected immune hemolysis. In patients with warm AIHA, small spherocytes are observed that represent splenic remodeling of antibody coated RBCs. Presence of complement on the surface of the RBC may also induce spherocyte formation. In cold reactive AIHA, spherocytes are less frequently observed. RBC agglutination can be observed in room temperature in cases of CAS. Blood film made at 37°C shows reversal of this agglutination due to dissociation of the antibody from the red cells. Polychromasia (reticulocytosis), teardrop cells, anisopoikilocytosis and erythrophagocytosis are other features observed in peripheral smear in up to 10% of children with AIHA. Reticulocytopenia may be observed. Autoantibody acting against erythroid precursors in the bone marrow, immune mediated clearance by the macrophages in the bone marrow and coexistent parvovirus B19 infections are explanations for the unusual finding of reticulocytopenia.

Bone marrow aspiration and biopsy are generally not required for diagnosis of AIHA. However, it may be done in patients with suspicion of bone marrow failure or malignancies. If done in AIHA, bone marrow reveals erythroid hyperplasia and mild dyserythropoiesis.

Urine examination is helpful in patients who present with high colored urine. Presence of hemoglobin in the urine in the absence of red cells indicates intravascular hemolysis. In patients with chronic hemolysis, hemosiderin may be observed in the urine. Biochemical investigations reveal unconjugated hyperbilirubinemia, elevated lactate dehydrogenase and aspartate aminotransferase and low serum haptoglobin.

The most important laboratory diagnosis in patients with AIHA is the demonstration of the RBC autoantibodies and their characteristics. *Direct agglutinin test* or *Coombs test* demonstrates membrane bound immunoglobulins or fragments of complement on patient's RBCs (**Figs 1 and 2**). Polyspecific direct antiglobulin test (DAT) is done initially using antihuman gamma globulin reagent. A thorough understanding of the procedure of DAT is vital in interpreting the results and deciding further treatment. Anticoagulated RBCs from the patient are washed several times

Table 2 Pathogenesis of drug-induced autoimmune hemolytic anemia (AIHA)

1. <i>Hapten and drug adsorption mechanisms</i> : Penicillins, cephalosporins, tetracycline, oxaliplatin, tolbutamide
2. <i>Immune/tertiary complex mechanisms</i> : Metformin, quinine, quinidine, cephalosporins, amphotericin b, rifampicin, thiopental, probenecid, diclofenac and doxepin
3. <i>Autoantibody mechanism</i> : Cephalosporins, tolmetin, α-methyldopa, L-dopa, mefenamic acid, cladribine, fludarabine, lenalidomide, procainamide, diclofenac
4. <i>Nonimmunologic protein adsorption</i> : Cephalosporins, carboplatin, cisplatin
5. <i>Unknown methods of AIHA causation</i> : Phenacetin, insecticides, chlorpromazine, acetaminophen, ibuprofen, thiazides, omeprazole, carboplatin, nalidixic acid, erythromycin, streptomycin

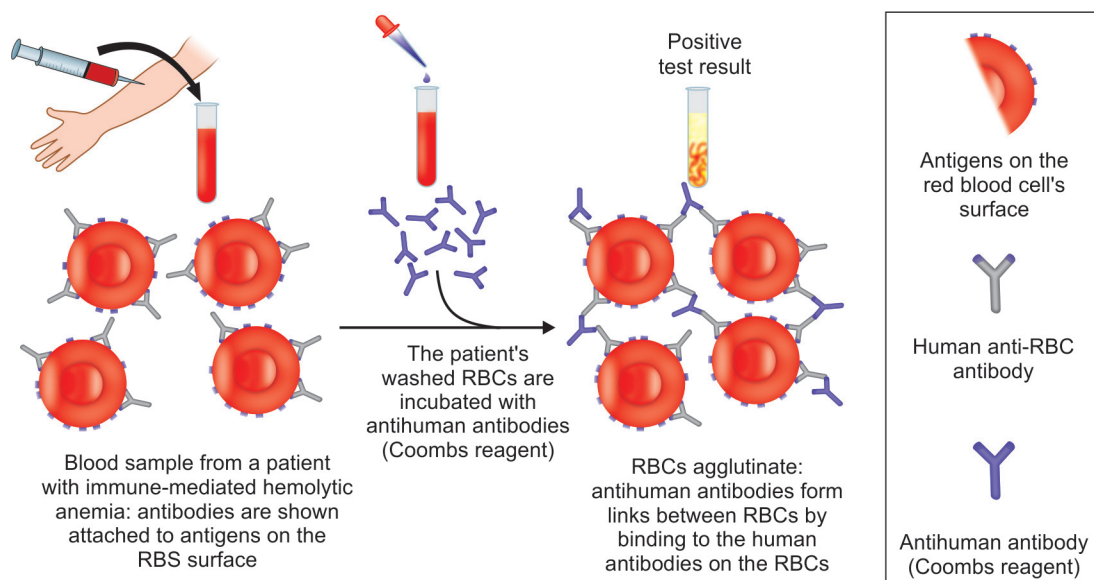


Figure 1 Direct Coombs test/direct antiglobulin test

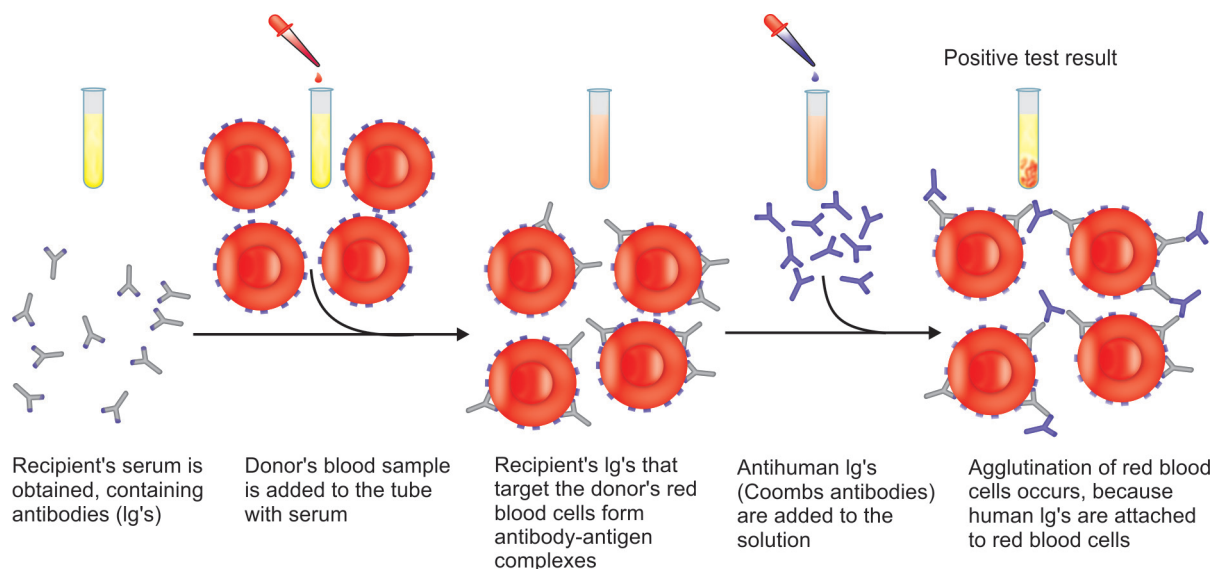


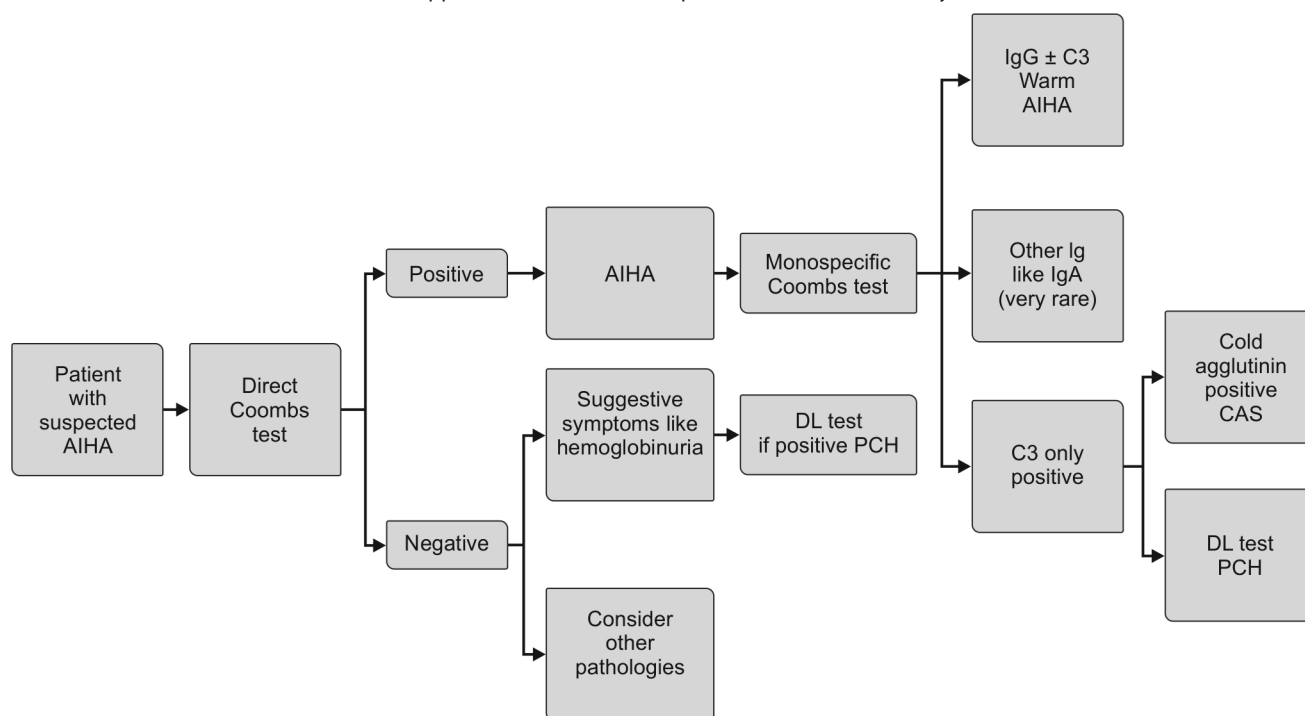
Figure 2 Indirect Coombs test/indirect antiglobulin test

to remove the plasma proteins and then incubated with Coombs reagent at 37°C. Coombs reagent contains polyclonal antiserum that is derived from rabbits that is directed against human IgG and human complement. This broad spectrum Coombs reagent helps to bridge the gap between autoantibodies on the surface of red cells. Indirect antiglobulin test detects antibodies in the serum of the patient. The detailed procedure of the test is depicted in **Figures 1 and 2**. In patients who are polyspecific DAT positive, monospecific DAT should be done to further elucidate the immunoglobulin or fraction of complement. IgG subclass determination helps more in prognostication. The vast majority of IgG antibodies are IgG1 subclass (> 70%) followed by IgG3.

Positive DAT with polyspecific Coombs reagent needs further discrimination between IgG and complement on RBC surface. The presence of IgG on the RBC with or without complement is

suggestive of warm reactive AIHA. The presence of complement alone needs to be further delineated into CAS or PCH. Serum of the patient needs to be analyzed for the presence of IgM autoantibody or IgG Donath-Landsteiner antibody. Performing the test at 37°C, 4°C, 10°C and room temperature further helps in characterizing the thermal reactivity of the antibody. DAT is scored on a scale of 1 to 4 based on the amount of agglutination. Approach to a child with suspected AIHA is detailed in **Flow chart 1**.

IgG positive DAT is typical of warm AIHA. Over 95% of warm AIHA have a positive DAT and this is consistent with the high prevalence of IgG. Among patients with warm AIHA, up to 60% have IgG antibodies alone on the RBC surface, 20–60% have IgG and C3, and 7–14% have only C3 on the RBC surface. Complement is not fixed tightly to the RBCs and thus helps to confirm warm AIHA.

Flow chart 1 Approach to a child with suspected autoimmune hemolytic anemia

Abbreviations: AIHA, autoimmune hemolytic anemia; PCH, paroxysmal cold hemoglobinuria; CAS, cold agglutinin syndrome; DL test, Donath-Landsteiner test

Direct antiglobulin test is more homogeneous in patients with CAS. Most patients have positive DAT due to the C3 on the RBC surface. Presence of IgM in the serum of the patients is suggestive of cold AIHA. This is usually accompanied by agglutination of RBCs in room temperature, which is reversed on warming. DAT demonstrates anti-C3 in patients with cold agglutinin disease. Cold autoantibodies react more at 0–4°C than at higher temperatures. The thermal amplitude and titer of the antibody is important as it predicts the degree of hemolysis. Larger thermal amplitude with activity noted at 37°C is always clinically significant. Most cold autoantibodies show specificity against the I/i antigen on the RBC surface.

Paroxysmal cold hemoglobinuria (PCH) is caused by a biphasic hemolysin that fixes complement to RBC at lower temperature but ultimately dissociates at higher temperature. Thus the DAT is positive for anti-C3, but negative for IgG at room temperature. In cases where DAT is positive due to C3 and is negative due to IgG, then further demonstration of the thermal reactivity is needed to differentiate between PCH and cold agglutinin disease. Donath-Landsteiner test (DL test) is done to demonstrate the biphasic hemolysis observed in PCH. The IgG autoantibody in this case, binds to RBCs and fixes complement at 4°C, but on warming to 37°C the complement cascade gets amplified and this leads to hemolysis. Two samples of the patient are kept at 37°C and centrifuged and serum is separated. This is then incubated with normal RBCs and a source of complement in a melting ice bath and at 37°C. Both these reactions are then again warmed to 37°C. In the sample that had cold incubation with complement, RBC lysis occurs due to binding of the antibody to RBCs and fixing of complement. In the sample that continued to be at 37°C, there is no lysis due to absent complement fixation. The actual incidence of PCH in childhood AIHA is a matter of debate. Up to 30–60% of children with AIHA have been reported in various studies as having PCH. Often PCH is not diagnosed because DL test is not ordered routinely, many

patients have negative DAT, DL test may become negative after few days and may be falsely negative if not done correctly.

Demonstration of autoantibodies that are active both at 37°C and 0–10°C are characteristic of mixed AIHA. Another observation is the presence of RBC agglutination on a peripheral smear along with positive DAT due to both IgG and C3. The red cells typically demonstrate pan reactive warm IgG antibody and the cold autoantibody against I/i antigen. In cases with drug-induced AIHA, serological diagnosis with DAT is similar to that by observed in warm AIHA. The diagnosis can be confirmed only on improvement observed on withdrawing the drug.

Drawbacks of DAT include the nonavailability of proper personnel for conducting the test, cost and the fact that it is subject to observer variation. Also, up to 10% of DAT may be falsely negative. This may be due to less density of immunoglobulins on the surface of RBCs, immunoglobulins other than IgG such as IgA, monomeric IgM and also due to technical errors. Manual DAT requires 100–500 molecules of IgG per red cell and around 400–1,100 molecules of C3d per red cell. Smaller amounts may need to be identified in some cases at diagnosis and also for following up the progress. In such cases, more sensitive techniques like enzyme linked DAT, column agglutination technology, flow cytometry and gel cards are helpful. Flow cytometry is the most sensitive of these tests and can detect even up to 35 IgG molecules per red cell.

DIFFERENTIAL DIAGNOSIS

In patients who present with anemia and jaundice, hemolytic anemia should be suspected and other causes such as microangiopathy, membrane defects and G6PD deficiency should be ruled out. In patients with positive osmotic fragility test and spherocytosis, DAT is usually done to rule out AIHA. In cases where reticulocyte count is less than expected, transient erythroblastopenia of childhood, aplastic anemia, bone marrow infiltration, etc., may be considered.

NATURAL HISTORY AND PROGNOSIS

In majority of children, the disease runs a short course and the prognosis is good. In general, cold reactive AIHA in children have a better outcome than warm AIHA. PCH runs a short course where aggressive supportive care is required. Warm AIHA may have a longer course with intermittent remissions and relapses. CAS in elderly has an indolent onset and runs a chronic course for years. Mortality in children with primary AIHA is less than 10% and more than 70% of patients have a self-limited disease. Mortality has been reported in children with chronic refractory disease probably with underlying ALPS or Evans syndrome. Factors that predict better prognosis in children include age between 2 years and 12 years, abrupt onset of symptoms, otherwise normal blood counts and lower number of reticulocytes than expected for the degree of anemia. Younger children or teenagers and those with indolent onset of symptoms tend to fare worse. Thus AIHA especially warm reactive, tends to resemble childhood immune thrombocytopenic purpura (ITP) in terms of pathogenesis, approach to treatment and prognosis. In a recent observational study from France, out of 265 children with AIHA, at a median follow-up of 3 years, it was observed that 4% children died, 285 were dependent on treatment and 39% were in complete remission. Isolated C3d positive AIHA was observed to have good prognosis IgG/IgG+C3d was associated with a lower rate of remission or survival.

TREATMENT

There are neither accepted guidelines nor definitions for response and refractoriness in AIHA. Supportive care in patients would include monitoring of vitals in children who present with cardiorespiratory compromise; transfusion of best cross-matched units as fast as possible and observation for features of intravascular hemolysis and renal shutdown. Folic acid supplementation is recommended in all, especially in warm AIHA.

Transfusing AIHA patients is often very challenging because of difficulties in ABO grouping and cross matching. Specialized tests such as allo or auto adsorption may often be required. At times it may be impossible to find a fully matched unit to transfuse. In such cases, *least incompatible* or *best matched* units may be transfused under supervision. Donor RBCs are destroyed at the same rate, as autologous RBCs. Antigen negative RBCs should be preferred in such cases. The likelihood of finding a cross matched unit is determined by the serological specificity of the antibody. In case of pan reactive antibody a proper cross-matched unit is often never found. Also, RBC units negative for I antigen and P antigen are difficult to obtain in cases of CAS and PCH respectively.

Patients with warm AIHA require immunosuppression to suppress the autoantibodies and reduce the immune hemolysis. Corticosteroids are the first line agents used. They inhibit the Fc receptor mediated clearance of sensitized erythrocytes and thus are effective within 24–48 hours of administration. They also inhibit autoantibody production, but this effect usually takes weeks. Oral prednisolone at 2 mg/kg/day or intravenous methyl prednisolone 1–2 mg/kg used 6–8 hourly may be used depending on the clinical condition. Up to 70% of children with warm AIHA respond initially to steroids and among them around 20% achieve a complete response. In these patients, steroids are tapered slowly over 2–3 months. However, steroid dependence is common and in almost one-third of the cases tapering of steroids is difficult. In patients who do not respond, or in whom tapering is not possible or in relapse, second line therapy is required. These include anti-CD20 monoclonal antibody rituximab, splenectomy or other immunosuppressive agents such as danazol, azathioprine,

cyclophosphamide, etc. Overall response after rituximab is up to 80%.

Intravenous immunoglobulin (IVIG) although an attractive option, demonstrates response only in a third of the warm reactive AIHA. Low pretreatment hemoglobin and hepatomegaly have been found to predict response to IVIG in few studies. Due to issues of cost, safety and less efficacy IVIG is not considered as a standard treatment for patients with AIHA. In patients who have recurrence after splenectomy or those who are not candidates for splenectomy, rituximab remains a reasonable alternative. Two-thirds of patients respond to splenectomy and remain transfusion free.

Cold agglutinin disease is more insidious and few patients require treatment. Keeping patients warm, wearing full sleeved clothing, covering the fingers and ears, giving blood and intravenous fluids using a blood warmer helps in reducing the extent of red cell agglutination and lysis. Using socks, earmuffs, mittens and moving to warmer climate help prevent development of acute hemolytic crisis. As most of the antibody is IgM and it remains intravascular, plasmapheresis is a treatment option in critical patients. IgM antibody being larger in size remains intravascular is amenable to removal by plasmapheresis. Also, IgM antibodies are less fixed to RBCs than IgG and are easily removed by pheresis. However, the extracorporeal circuit should be warmed in order to prevent exacerbation of agglutination. Steroids and splenectomy are less effective. Hemolysis is usually intravascular, if at all extravascular is usually the liver. Rituximab may be used in acutely ill symptomatic patients. Rituximab shows a response in up to 50% of patients treated and the median duration of remission is 11 months. Combination of rituximab and fludarabine although more toxic, has also been reported to show response in up to 75% patients. Cyclophosphamide, chlorambucil, interferon, etc., are agents that have been found beneficial in CAS. Eculizumab, traditionally used in patients with paroxysmal nocturnal hemoglobinuria has been studied in patients with CAS and shown to reduce hemolysis by blocking the C5 complement.

Treatment of PCH is only supportive as most cases are self-limited. In drug induced AIHA, removal of the offending drug is often the only treatment required. Steroids are not required and other treatment modalities discussed earlier are also of questionable benefit. Occasionally it may take months of removal of the drug in order to get a complete resolution.

Management of chronic refractory AIHA is often very difficult, there are no accepted algorithms or practice guidelines. Treatment is often individualized based on the hematological response and side effect profile. Rituximab is a relatively safe option for chronic patients. Rituximab eliminates circulating B-cells, thus eliminating the autoreactive B-lymphocytes.

IN A NUTSHELL

1. Autoimmune hemolytic anemia (AIHA) is an uncommon disorder in children with varying severity.
2. The diagnosis is based upon immune-hematological investigations including characterization of autoantibodies.
3. Grouping and cross matching pack cell transfusion is difficult. Most compatible leukodepleted blood should be transfused under close supervision.
4. Steroids are first line of therapy.
5. Rituximab is relatively safe and it eliminates circulating autoreactive B-lymphocytes.
6. Immunosuppressive drugs may be used in children who fail to respond to steroids.
7. Children with AIHA required long-term follow-up.

MORE ON THIS TOPIC

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Chapter 38.15

Physiology of Hemostasis

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Hemostasis refers more widely to the process whereby blood coagulation is initiated and terminated in a tightly regulated fashion, together with the removal of the clot as part of vascular remodeling. Hemostasis preserves vascular integrity by balancing the physiologic processes that maintain blood in a fluid state under normal circumstances and prevent excessive bleeding after vascular injury. It depends on an intact vascular endothelium and a complex series of regulatory pathways that maintain platelets in a quiescent state and keeps the coagulation system in check.

Vascular damage begins with the initiation of clotting with the goal of producing a localized fibrin-platelet plug to prevent blood loss: this action is followed by processes that lead to clot containment, wound healing, clot dissolution, tissue regeneration and remodeling. In healthy persons, all these reactions occur simultaneously and in a balanced fashion, such that bleeding is contained, yet blood vessels simultaneously remain patent to deliver adequate organ blood flow. When any of these hemostatic processes is disrupted, because of inherited defects or acquired abnormalities, disordered hemostasis may result in bleeding or thrombosis.

Blood flow in the arterial and venous system is disparate and imposes different needs on the coagulation system. In the pressurized arteries, relatively minor vascular damage can result in massive blood loss, the procoagulant response in arteries must rapidly arrest bleeding. Platelets are critical to this arterial response. They initially limit blood loss and then provide an active surface for soluble clotting factors to both localize and accelerate fibrin clot formation. By contrast, in the venous circulation, the slower flow rates produce slower bleeding, a feature that makes platelets less critical. Instead controlling the balance of the venous system is most dependent on the rate of thrombin generation.

The four major components of the hemostatic system are the vascular endothelium, platelets and the coagulation and the fibrinolytic systems (**Fig. 1**). The general sequence of events in hemostasis at a site of vascular injury are:

- Endothelial injury exposes highly thrombogenic subendothelial extracellular matrix (ECM), facilitating platelet adherence and activation. Activation of platelets results in shape change, as well as the release of secretory granules. Within minutes the secreted products recruit more platelets for aggregation to form a hemostatic plug; this process is referred to as *primary hemostasis*.
- Tissue factor (TF) is also exposed at the site of injury. It is a membrane-bound procoagulant glycoprotein synthesized by endothelial cells (ECs). It acts in association with factor VII as the major *in vivo* initiator of the coagulation cascade, eventually resulting in thrombin generation. Thrombin cleaves circulating fibrinogen into insoluble fibrin, creating a fibrin meshwork, and also induces additional platelet recruitment and activation. This sequence, *secondary hemostasis*, consolidates the initial platelet plug.
- Polymerized fibrin and platelet aggregates form a solid, permanent plug to prevent any further hemorrhage. At this stage, counter-regulatory mechanisms [e.g., tissue plasminogen activator (t-PA)] are set into motion to limit the hemostatic plug to the site of injury (*tertiary hemostasis*).

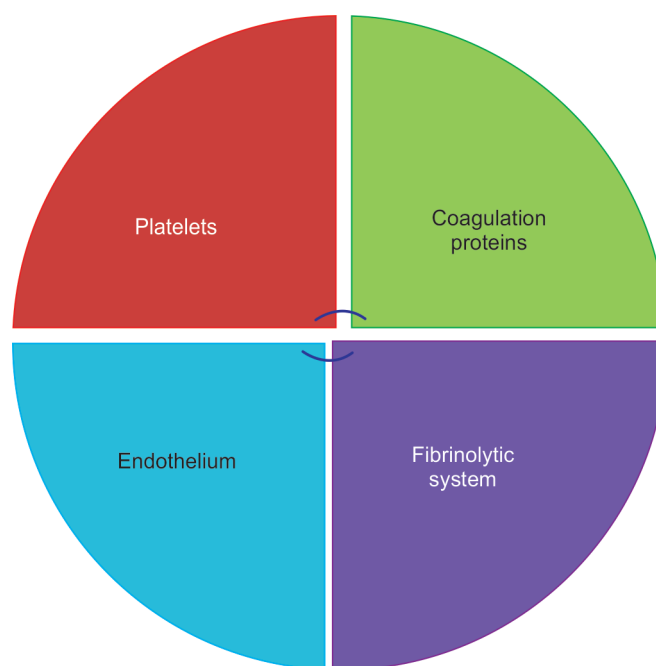


Figure 1 Four important components of the hemostatic system

VASCULAR ENDOTHELIUM

The endothelium forms a continuous monolayer at the interface between blood and tissue, contributing significantly to sensing and transducing of signals and maintenance of a nonthrombogenic surface permitting flow of blood. It is a dynamic organ that actively regulates hemostasis by inhibiting platelet aggregation, suppressing the activation and propagation of coagulation, enhancing fibrinolysis and modulating vascular tone and permeability. Conversely, when injured or under inflammatory conditions, the endothelium may become procoagulant. Defective vascular function can lead to bleeding if the endothelium becomes more permeable to blood cells, if vasoconstriction does not occur, or if premature degradation of hemostatic plugs opens seals in the vasculature. The anticoagulant functions of endothelium are (**Fig. 2A**):

Platelet Inhibition

Endothelial cells (EC) synthesize prostacyclin and nitric oxide which serve as potent vasodilators and also inhibit platelet activation and subsequent aggregation by stimulating adenylate cyclase and increasing the intracellular levels of cyclic adenosine monophosphate (cAMP). In addition, ECs also express CD39, which is a membrane associated ADPase. It attenuates platelet activation by inhibiting adenosine diphosphate (ADP), which is a platelet agonist.

Anticoagulant Action

Endothelial cells use three important mechanisms to inhibit thrombin generation and limit coagulation. Heparin sulfate proteoglycans secreted into the luminal surface of ECs, are capable of binding and activating antithrombin III, thus accelerating the inactivation of thrombin, factor Xa and factor IXa. Thrombomodulin on the surface of ECs binds thrombin. Once bound, the thrombin-thrombomodulin complex gains the ability to activate protein C to its active form-activated protein C (APC). APC, along with its cofactor protein S, phospholipid surface and calcium ions, acts to down-regulate thrombin generation by proteolyzing factor Va and factor

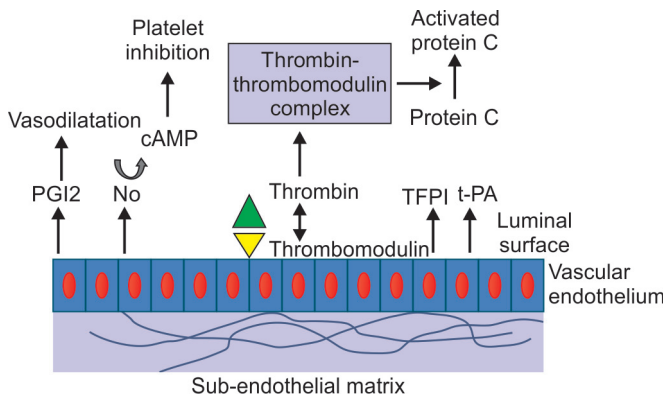


Figure 2A Depicts the anticoagulant properties of the vascular endothelium

Abbreviations: PGI₂, prostacyclin; NO, nitrous oxide; cAMP, cyclic adenosine monophosphate; TFPI, tissue factor pathway inhibitor; t-PA, tissue plasminogen activator

VIIIa. ECs synthesize tissue factor pathway inhibitor (TFPI), which is a serine protease inhibitor, that modulates TF initiated coagulation by directly inhibiting the TF-factor VIIa-factor Xa complex.

Fibrinolytic Activity

The vascular endothelium promotes fibrinolysis by synthesizing and releasing tissue-type and urokinase-type plasminogen activator (t-PA and u-PA), which initiate fibrinolysis by converting plasminogen (PLG) into plasmin.

Perturbation of the vascular lining by inflammatory mediators such as interleukin-1, tissue necrosis factor, converts the endothelium from a nonthrombogenic to a procoagulant surface by down-regulating the anticoagulant mechanisms and shifting the equilibrium towards procoagulant properties (**Fig. 2B**).

Platelet Activation

When endothelium is physically damaged or becomes activated, the balance of coagulant properties is shifted to procoagulant state. This function is mediated by endothelium and the underlying subendothelial matrix that is exposed by vascular injury. Activated endothelium expresses adhesive ligands on their surface including selectins, beta 1 and beta 2 integrins and von Willebrand factor (vWF) multimers. On the endothelial surface, vWF multimers localize and promote platelet adhesion whereas integrins mediate adhesion and subsequent transendothelial migration of leukocytes into the tissues. Exposed subendothelial matrix also bind vWF multimers and contain other adhesive procoagulant proteins, i.e., thrombospondin, fibronectin and collagen, which serve as ligands to capture platelets. Collagen, in particular is a platelet ligand and as well as platelet agonist. It causes platelets to undergo dense granule release and to express conformationally active ligands such as glycoprotein IIb/IIIa.

Procoagulant Effects

In response to cytokines or bacterial endotoxin, ECs synthesize *TF*, the major activator of the extrinsic clotting cascade, which is constitutively expressed by subendothelial muscle cells and fibroblasts. In addition, activated ECs augment the catalytic function of activated coagulation factors IXa and Xa.

Antifibrinolytic Effects

It also produces type I plasminogen-activator-inhibitor (PAI-I). Which is the major regulator of t-PA and u-PA. It blocks the ability

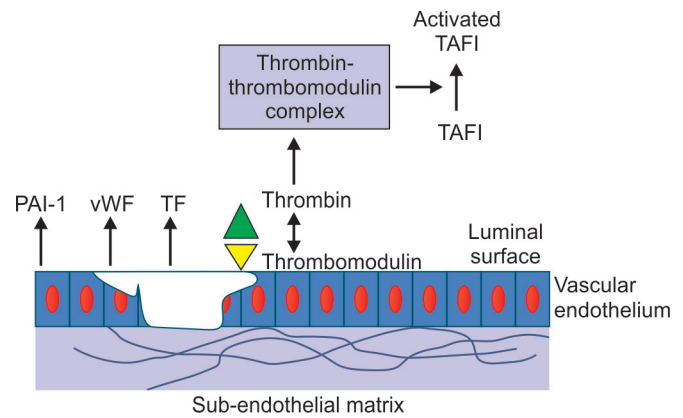


Figure 2B Depicts the procoagulant functions of the vascular endothelium in response to injury

Abbreviations: TAFI, thrombin-activatable fibrinolytic inhibitor; PAI-1, plasminogen-activator-inhibitor-1; vWF, von Willebrand factor; TF, tissue factor

of t-PA to turn on plasmin, the primary enzyme of fibrinolysis. Also, the thrombin-activatable fibrinolytic inhibitor (TAFI) is cleaved to its active form by the thrombin-thrombomodulin complex on endothelial surface which further catalyzes the removal of lysine residues from the fibrin clot, making it less recognizable as a substrate for plasmin. Fibrinolysis localizes to the endothelial surface because these cells express annexin II, which acts as a coreceptor for PLG and t-PA and promotes their interaction.

PLATELETS

Platelets are discoid anucleate particles arising from megakaryocytes in the bone marrow that play a critical role in hemostasis and thrombosis. Platelets ordinarily circulate in the bloodstream in a quiescent state but undergo *explosive* activation following damage to the vessel wall, leading to rapid formation of a platelet aggregate or vascular plug and occlusion of the site of damage. Damage to the intimal lining of the vessel exposes the underlying subendothelial matrix. Platelets home to such sites of vascular disruption and adhere to the exposed matrix proteins. Adherent platelets undergo activation and release substances that recruit additional platelets to the site of injury as well as promote thrombin generation and fibrin clot formation.

Platelet Adhesion

Platelets adhere to exposed collagen and vWF and form a monolayer that supports fibrin formation. It depends upon constitutively expressed receptors on the platelet surface, $\alpha 2\beta 1$ and glycoprotein VI, which bind collagen and GPIIb/IIIa, which bind vWF. vWF is synthesized by ECs and megakaryocytes and assembles into multimers.

When released from Weibel-Palade bodies of the ECs or α -granules of platelets, most of the vWF enters the circulation but the vWF released from the abluminal surface of the ECs accumulates in the subendothelial matrix, where it binds collagen via its A3 domain. This surface-immobilized vWF can simultaneously bind platelets via its A3 domain. The larger vWF multimers provide additional binding sites for collagen and enhance platelet adhesion because platelets have higher vWF receptors than collagen receptors.

Platelet Activation and Secretion

Adhesion to collagen and vWF initiates signals leading to platelet activation, mainly cyclooxygenase dependent synthesis and

release of thromboxane A₂, and the release of ADP from storage granules, which recruit platelets to the site of injury. To activate platelets, both thromboxane A₂ and ADP must bind to their own G-protein-coupled receptors (TP and P2Y₁₂), respectively. This results in an increase in the intracellular calcium concentration within the platelets, thus inducing a shape change. Shape change is mediated by phosphorylation of myosin light chains, either as a consequence of elevation in intracellular Ca²⁺ ions, which activate myosin light chain kinase, or through inhibition of myosin light chain phosphatase, which is regulated downstream of Rho kinase.

Activated platelets promote coagulation by expressing phosphatidylserine on their surface, which is an anionic phospholipid that supports assembly of coagulation factor complexes, thereby triggering thrombin generation and subsequent fibrin formation. They also cause stabilization of clot by releasing factor V, factor XI, fibrinogen and factor XIII.

Activated platelets also release vWF, fibronectin and thrombospondin which may augment platelet adhesion at sites of injury as well as platelet-derived growth factor (PDGF) and transforming growth factor-beta (TGF-β), which promote wound healing.

Platelet Aggregation

Platelet aggregation links platelets to form clumps. GPIIb/IIIa mediates these platelet to platelet linkages. On nonactivated platelets, GPIIb/IIIa exhibits minimal affinity for its ligands. Upon platelet activation, GPIIb/IIIa undergoes a conformational change, which reflects transmission of inside-out signals from its cytoplasmic domain to its extracellular domain, enhancing its affinity for ligands such as fibrinogen and vWF. Arginine-glycine-aspartic acid (RGD) sequences on fibrinogen and vWF as well as platelet binding lysine-glycine-aspartic acid (KGD) sequence on fibrinogen mediate their interaction with GPIIb/IIIa, divalent fibrinogen and multivalent vWF molecules serve as bridges to and bind adjacent platelets together. After being bound to GPIIb/IIIa, fibrinogen and vWF induce signals that augment platelet activation and result in activation of additional GPIIb/IIIa receptors, creating a positive feedback loop.

COAGULATION CASCADE

Coagulation results in the generation of thrombin, which converts soluble fibrinogen into an insoluble fibrin clot. Coagulation occurs through the action of discrete enzyme complexes, which are composed of a vitamin K-dependent enzyme and a nonenzyme cofactor, and assemble on anionic phospholipid membranes in a calcium-dependent manner. The important enzyme complexes involved in thrombin generation include extrinsic tenase, intrinsic tenase and prothrombinase complex comprising of TF-VIIa-IX-X, VIII-IXa-X, and V-Xa-II respectively.

Factors II, VII, IX, and X (as well as proteins C, S, and Z) are the zymogen forms of vitamin K-dependent serine proteases. Vitamin K is a necessary cofactor for a post-translational modification that adds a carboxyl group to the 10–12 glutamic acid residues in the amino terminal portion of each of these proteins. The vitamin K-dependent proteins utilize these clusters of γ-carboxyl glutamic acid (Gla) residues to adhere to phospholipid surfaces and assemble multimolecular coagulation complexes. Without this important post-translational modification, the assembly of cell-based coagulation complexes is impaired, leading to ineffective fibrin formation. Calcium and phospholipid (a platelet membrane constituent) are required for the tenase and prothrombinase complexes to function. Calcium mediates the binding of the complexes via the terminal gamma-carboxy residues on FXa and FIXa to the phospholipid surfaces expressed by platelets, as well as procoagulant microparticles or microvesicles shed from them. Calcium is also required at other points in the coagulation cascade.

Table 1 shows the list of all the coagulation proteins involved in formation of a fibrin clot.

Blood coagulation is traditionally classified into *extrinsic* and *intrinsic* pathways that converge on the activation of factor X (**Fig. 3**). The extrinsic pathway was so designated because it required the addition of an exogenous trigger (originally provided by tissue extracts); the intrinsic pathway only required exposing factor XII (Hageman factor) to thrombogenic surfaces (even glass would suffice). However, such a division is largely an artifact of in vitro testing; there are, in fact, several interconnections between the two pathways. Moreover, the extrinsic pathway is the most physiologically relevant pathway for coagulation occurring when vascular damage has occurred; it is activated by *TF* (also known as *thromboplastin* or factor III), a membrane-bound lipoprotein expressed at sites of injury. *TF* initiated coagulation has two phases—an initiation phase and propagation phase.

Initiation Phase

It begins as the exposed *TF* binds to activated VIIa, in a 1:1 ratio, picomolar amounts of which is in the circulation at all times to form extrinsic tenase complex (*TF*-VIIa). This complex catalyzes the conversion of very small amounts of *FX* to *FXa*, which in turn generates nanomolar amounts of thrombin. Extrinsic tenase activates factor X and IX to their activated forms through cleavage of an activation peptide. This seemingly trivial amount of thrombin during the initiation phase sparks the inception of the propagation phase, successful completion of which results in extensive thrombin generation and fibrin deposition. Once the pathway commences, the *TF*/factor VIIa activation of factor X is rapidly shut down by an inhibitor produced by ECs, *TFPI*.

Table 1 List of coagulation proteins involved in the formation of a fibrin clot

Coagulation proteins	Function
Fibrinogen (Factor I)	Adhesive protein that forms the fibrin clot
Prothrombin (Factor II)	Main enzyme of coagulation in activated form
Tissue factor (Factor III)	Initiator of extrinsic pathway
Calcium ions (Factor IV)	Metal cation necessary for coagulation reactions
Factor V (labile factor)	Cofactor for activation of prothrombin to thrombin
Factor VII (proconvertin)	Initiates extrinsic pathway with tissue factor
Factor VIII (antihemophilic factor)	Cofactor for intrinsic activation of factor X
Factor IX (Christmas factor)	Enzyme for intrinsic activation of factor X
Factor X (Stuart-Prower factor)	Enzyme for final common pathway activation of prothrombin
Factor XI (plasma thromboplastin antecedent)	Intrinsic activator of factor IX
Factor XII (Hageman factor)	Starts aPTT-based intrinsic pathway
Factor XIII (fibrin stabilizing factor)	Transamidase that cross links fibrin clot
High molecular weight kininogen	Cofactor
Prekallikrein (Fletcher factor)	Acts at the beginning of aPTT-based intrinsic pathway

Abbreviation: aPTT, activated partial thromboplastin time.

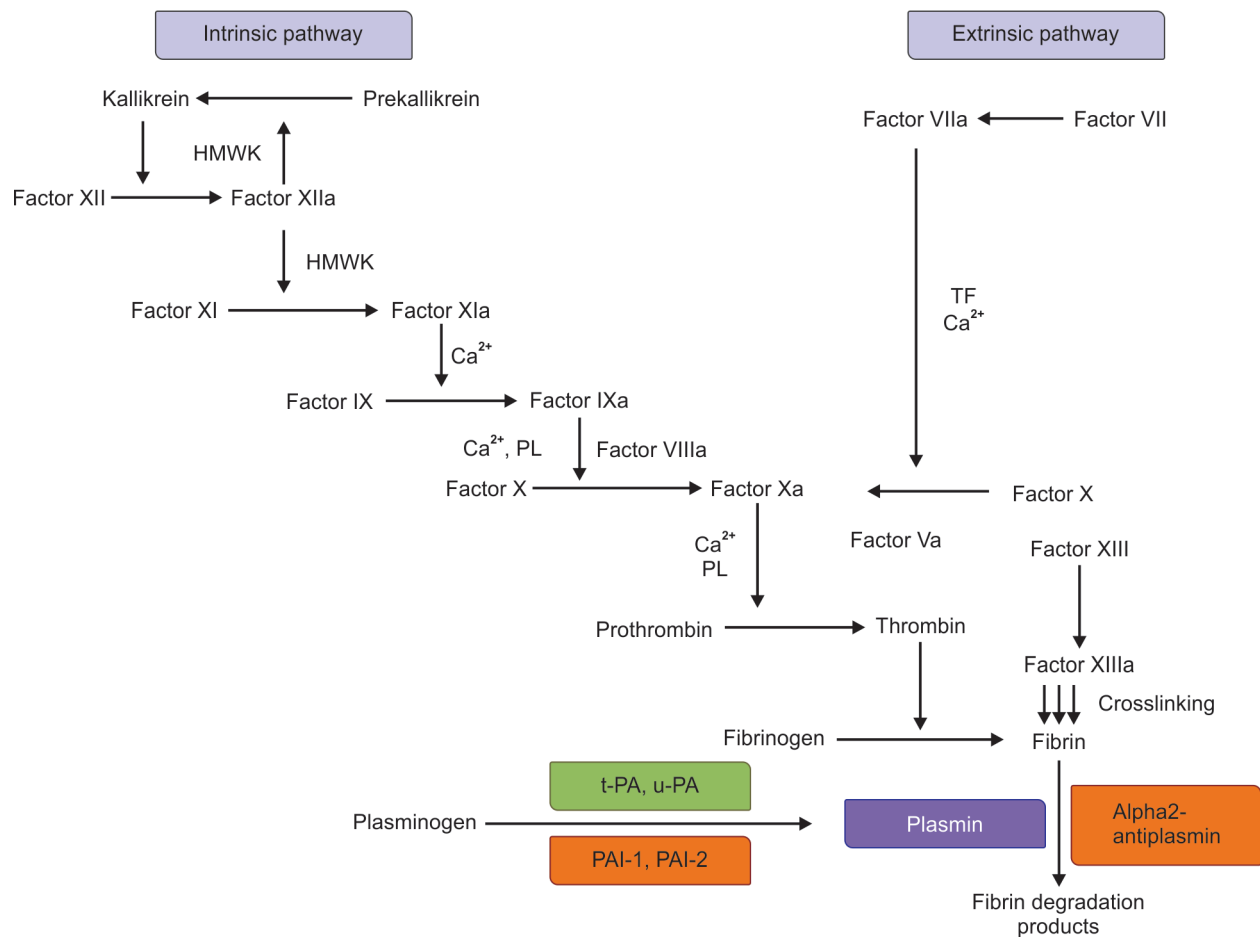


Figure 3 Coagulation and fibrinolytic pathways

Inhibitory proteins are indicated in orange

Abbreviations: HMWK, high molecular weight kininogens; Ca²⁺, calcium; PL, phospholipids; TF, tissue factor; t-PA, tissue plasminogen activator; u-PA, urokinase plasminogen activator; PAI-1, plasminogen activator inhibitor 1; PAI-2, plasminogen activator inhibitor 2.

Propagation Phase

Thrombin generated during the initiation phase is a potent platelet activator supplying the developing clot with a activated platelet surface membrane and abundant platelet-released factor V which is promptly activated to Va by thrombin. Factor VIII, conveniently shifted to the bleeding site by its carrier vWF, is also activated by thrombin. Factor VIII then complexes with picomolar amounts of FIXa generated by TF-VIIa complex during the initiation phase to create FVIIIa-FIXa complex (intrinsic tenase complex). Formation of this complex on the platelet surface heralds the switch of the primary path of Xa generation from extrinsic tenase (TF-VIIa) to intrinsic tenase (VIIIa-IXa). This has significant kinetic advantage, with intrinsic pathway exhibiting 50 fold higher efficiency than the extrinsic pathway.

The activation of factor X-Xa starts the final, common pathway for thrombin activation. Factor Xa combines with the cofactor, factor Va, together with calcium on phospholipid surfaces to form the prothrombinase complex. This complex then effects the conversion of prothrombin to thrombin by cleavage of an activation peptide, prothrombin F 1.2. Activation of factors V and VIII by thrombin results in a further burst of coagulation activity through increased activity of the tenase and prothrombinase complexes.

Fibrinogen is the ultimate substrate protein of the coagulation cascade and forms the principal structural protein of the fibrin clot. Fibrinogen, produced in the liver, is a dimer composed of three pairs of protein chains, A α , B β , and γ , that are disulfide

linked at their N-terminal ends. Thrombin cleaves small peptides, termed fibrinopeptides A and B, from the A α and B β chains, respectively, to form a fibrin monomer. These monomers assemble into protofibrils in a half-staggered, side-to-side fashion that is stabilized by noncovalent interactions between fibrin molecules. The protofibrils laterally associate into thicker fibrin fibers and form the fibrin clot. This clot, however, is not stable and ultimately will come apart if not covalently cross-linked. Thrombin activates factor XIII to the transglutaminase enzyme factor XIIIa. Factor XIIIa, acting upon the glutamic acid and lysine side chains in the fibrin amino acid sequence, creates covalent bonds between fibrin monomer γ chains, creating a stable clot.

Once activated, the coagulation cascade must be restricted to the site of vascular injury to prevent runaway clotting of the entire vascular tree. Besides restricting factor activation to sites of exposed phospholipids, three important categories of endogenous anticoagulants also control clotting (**Table 2**).

- Antithrombins (e.g., antithrombin III) inhibit the activity of thrombin and other serine proteases, including factors IXa, Xa, XIa, and XIIa. Antithrombin III is activated by binding to heparin-like molecules on ECs.
- Proteins C and S are vitamin K-dependent proteins that act in a complex that proteolytically inactivates factors Va and VIIIa. Protein C activation by thrombomodulin was described earlier.
- TFPI is a protein produced by endothelium (and other cell types) that inactivates TF-factor VIIa complexes.

Table 2 List of blood coagulation regulatory molecules

Regulatory proteins in coagulation	Function
Protein C	Anticoagulant protease
Protein S	APC cofactor and coagulation inhibitor
Thrombomodulin	Receptor for protein C/thrombin
Endothelial protein C receptor	Receptor for protein C/APC
Protease activated receptor-I	G-protein coupled inhibitor
Antithrombin	Protease inhibitor
Tissue factor pathway inhibitor	Protease inhibitor
Heparin cofactor-II	Protease inhibitor
Protein Z	Protease inhibitor
Protein Z-dependent protease inhibitor	Protease inhibitor

Abbreviation: APC, activated protein C.

FIBRINOLYTIC SYSTEM

Activation of the coagulation cascade also sets into motion a fibrinolytic cascade that moderates the size of the ultimate clot. Fibrinolysis initiates when PLG activators convert PLG into plasmin, which then degrades fibrin into soluble fragments (**Fig. 3**). Blood contains two immunologically and functionally distinct PLG activators, t-PA and u-PA. Whereas t-PA mediates intravascular fibrin degradation, u-PA binds to a specific u-PA receptor (u-PAR) on the surface of cells, where it activates cell-bound PLG. Pericellular proteolysis during cell migration and tissue remodeling and repair are the main functions of u-PA. Regulation of fibrinolysis occurs at two levels:

PAI-1 and PAI-2 Inhibit the Plasminogen Activators

Endothelial cells synthesize PAI-1, which inhibits both u-PA and t-PA whereas monocytes and placenta synthesize PAI-2, which specifically inhibits u-PA. PAI-1 inhibits its target proteinases by formation of a 1:1 stoichiometric reversible complex, followed by covalent binding between the hydroxyl group of the active site serine residue of the proteinase and the carboxyl group of the P1 residue of the serpin. Highly positively charged regions in t-PA and in u-PA are involved in the rapid interaction. PAI production is increased by thrombin as well as certain cytokines, and probably plays a role in the intravascular thrombosis accompanying severe inflammation.

α 2-Antiplasmin Inhibits Plasmin

It forms a stable 1:1 complex with plasmin, in which the protease is completely inactivated. In addition to inactivating preformed

plasmin, α 2-AP retards fibrinolysis by reducing PLG activation and by *masking* the lysine binding sites through which PLG interacts with fibrin.

IN A NUTSHELL

1. The coagulation pathway is a complex interaction of many elements—the endothelium, coagulation factors, and platelets—with the ultimate goals of stemming the loss of blood at the site of an injury and laying the groundwork for injury repair and healing.
2. Bleeding will occur if there is failure to seal vascular leaks because of defective hemostatic plug formation or their premature breakdown.
3. In contrast, thrombosis may occur if prothrombotic stimuli are unregulated. Control of coagulation reactions is essential for normal hemostasis.
4. Pathologic thrombosis occurs when the protective clot is extended beyond its beneficial size, when a clot occurs inappropriately at sites of vascular disease, or when a clot embolizes to other sites in the circulatory bed.
5. For normal hemostasis, both procoagulant and anticoagulant factors must interact with the vascular components and cell surfaces, including the vessel wall and platelets.
6. Moreover, the action of the fibrinolytic system must be integrated with coagulation reactions for timely formation and dissolution of blood clots.

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Chapter 38.16

Bleeding and Coagulation Disorders

Tulika Seth

A bleeding child is not an uncommon problem; this can occur in many ill or even apparently well looking children. Bleeding episodes cause fear and alarm to the child and family. The etiology of bleeding is varied and ranges from immune thrombocytopenia, medications which interfere with platelet function, inherited coagulation factor defects, to disseminated intravascular coagulation (DIC). Sometimes even bone marrow failure or an underlying malignancy may be the cause, and it is always of extreme urgency to identify the etiology and provide definitive treatment. Hence due to the vast etiological causes a good assessment and approach is needed to evaluate the child, so as to speedily reach a diagnosis and limit the number of tests.

Initial assessment of a bleeding patient involves evaluation of the vitals and hemodynamic status. Stabilization is a priority, as most tests can be performed even after fluid resuscitation or even blood transfusion, if necessary. Attempt to control the bleeding, if blood loss is significant and give fluid resuscitation. In presence of significant blood loss, packed red cell transfusions may be given. If a coagulation defect is suspected, promptly send samples for baseline coagulation tests and give fresh frozen plasma (FFP), to control the bleeding. If platelet dysfunction like Glanzmann thrombasthenia is suspected, give platelet transfusions after sending sample. If samples cannot be sent prior to FFP, it is important to stabilize child in a life threatening situation, the required tests can be performed later, in consultation with the hematologist.

EPIDEMIOLOGY AND ETIOLOGY

The causes of bleeding and coagulation disorders is extremely varied; it stretches from acquired nutritional deficiency like scurvy, to viral infections like dengue. From inherited disorders, like X-linked hemophilia A and B and rare factor autosomal recessive deficiency states like factor X and XIII deficiency, and platelet function disorders, to von Willebrand disease (vWD) an autosomal dominant condition. Bleeding can be associated with aplastic anemia, childhood malignancies and hepatic or renal dysfunction. DIC can be seen in children due to a wide variety of causes. The incidence of hemophilia A is about 1 in 5,000 boys, whereas the incidence of hemophilia B is less common about 1 in 30,000 boys. The incidence of many of the rarer factor deficiencies has little data from India, and many cases may go uninvestigated.

The true incidence of aplastic anemia and inherited bone marrow failure syndromes (IBMFS) is not known in India but is thought to be higher than that mentioned in western literature. Hence, it is important to have a high index of suspicion and follow the given algorithms so as to not miss a bleeding or coagulation disorder. Child abuse is often missed and unusual bruising and frenulum injury may point to nonaccidental trauma.

PATHOPHYSIOLOGY

The normal coagulation cascade (see chapter 38.15) requires all factors to be present in the normal range. Any defect can lead to disturbances in clotting (**Table 1**). Risk factors strongly associated with inherited hemophilia include family history (from the maternal side), male sex, and history of recurrent or severe

bleeding. Musculoskeletal bleeding is the hallmark of hemophilia. Low platelet count is seen in immune thrombocytopenic purpura (ITP), aplastic anemia, leukemia, etc. Adequate platelet number and function is also important to control bleeding.

CLINICAL FEATURES

Children with bleeding may have an inherited or acquired defect. A detailed bleeding history is an essential part of the work up, this includes the child's age at presentation, sex, clinical manifestation, past history and family history, response to prior trauma, minor surgery and medications. A detailed description of type of bleeding, sites, seriousness of bleeds and need for prior intervention for bleeding episodes is required to differentiate between platelet and coagulation disorders (**Table 2**). An excessive bleeding response to commonly encountered challenges suggests the possibility of an underlying bleeding disorder. Certain inherited genetic conditions (**Box 1**) are associated with bleeding; presence of phenotypic features may assist in suspecting such conditions, which can be confirmed by diagnostic tests (**Flow charts 1 and 2**). This helps in narrowing down the evaluation and identification of the possible defect in coagulation mechanism and prioritizing relevant diagnostic tests.

Mucocutaneous bleeds, such as petechiae, purpura, epistaxis and oral bleeding are characteristic of platelet and blood vessel disorders. Soft tissue, muscle or joint hematomas are suggestive of coagulation factor deficiency like hemophilia. Early childhood bleeding occurs most frequently in congenital disorders, while a later presentation is more likely to be associated with acquired disorders. A child who is clinically ill may have sepsis and DIC.

Acute massive mucocutaneous bleeding in a patient previously without symptoms should suggest ITP. Massive bruising and oozing from multiple sites in an otherwise asymptomatic patient might suggest accidental warfarin ingestion. Postoperative bleeding at a surgical site is usually related to a local surgical problem. Spontaneous or excessive post-traumatic bleed, if immediate, can indicate a localized pathologic process and if delayed after 2–3 days, without infection is usually due to a hemostatic deficiency, like hemophilia, even in mild hemophiliacs. Serious bleeding episodes including intracranial, massive gastrointestinal, bleeding in neck and retroperitoneal bleeds, need urgent investigation and warrant a complete coagulation workup. These sites of hemorrhage may not be diagnosed easily and can lead to shock and even death.

DIFFERENTIAL DIAGNOSES

The most common presentation of bleeding is epistaxis, but not every child with epistaxis needs a full coagulation disorder work up. Hence it is important to evaluate the child and see if this is a local problem or more sinister.

A typical episode of epistaxis in a child is usually minor bleeding, which resolves spontaneously or with pressure. It usually occurs on one side of nose only, rarely leads to anemia or hospitalization. No other sites of bleeding are present. Though, some cases may need repeated attention, if nose picking, repeated upper respiratory tract infections or if Little's area is affected. They show good response to cautery, local application of vasoconstrictor or nasal packing. If there is profuse bleeding or it persists despite nasal packing, the child is more likely to have a coagulopathy. Also, the child is more likely to have either coagulation or bleeding defect if other sites of bleeding and ecchymoses are present. Possible causes of coagulopathy include primary disorders of coagulation (e.g., hemophilia, vWD), liver disease, and medicines that impair clotting [e.g., aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), warfarin].

Table 1 Conditions associated with abnormal coagulation assays

Condition	Platelet count	Prothrombin Time	aPTT	Thrombin time	Other tests
Hemophilia A or B	Normal	Normal	Prolonged	Normal	Specific assay for factor VIII or IX
von Willebrand disease	Normal decreased in type 2 N	Normal	Prolonged or normal	Normal	Platelet function assay Factor VIII and vWF low and impaired ristocetin-induced platelet aggregation
Disseminated intravascular coagulopathy	Low	Prolonged	Prolonged	Grossly prolonged	D-dimer and FDP raised
Massive transfusion	Low	Prolonged	Prolonged	Normal	
Oral anticoagulants (Warfarin)	Normal	Grossly prolonged	Prolonged	Normal	
Liver disease	Low	Prolonged	Prolonged	Normal (rarely prolonged)	Liver function tests abnormal
Unfractionated Heparin	Normal (rarely low)	Normal	Prolonged	Prolonged	
Low molecular weight heparins	Normal	Normal	Normal	Normal	Specific anti-Xa assay, needs monitoring in neonates and in presence of renal dysfunction.

Table 2 Differentiation of mucosal versus deep bleeding by historical facts in patients with suspected coagulation or platelet disorders

Pertinent questions	Deep bleeds (coagulation factor disorders)	Mucosal bleeding (Platelet disorders and von Willebrand disease)
Hemarthrosis, muscle bleeds	Very common	Rare
Bruising on trunk and limbs	Large bruises	Small bruises, petechiae (rarely large if due to trauma)
Bleeding from cuts	Relatively slight	Profuse
Nosebleeds, oral bleeds, history of heavy menstrual bleeding	Uncommon	Common, frequently profuse and of long duration
Bleeding after surgery or dental extraction	After 1 or 2 days	Immediate
Gastrointestinal bleeding	Uncommon	Common
Hematuria	Common	Rare

BOX 1 Clinical syndromes associated with inherited bleeding disorders**Thrombocytopenia**

1. Wiskott-Aldrich syndrome—eczema, immunodeficiency and thrombocytopenia
2. Thrombocytopenia with absent radii, amegakaryocytic thrombocytopenia with radioulnar synostosis skeletal defects
3. DiGeorge/velocardiofacial syndrome—cleft palate, cardiac defects, facial anomalies, learning disabilities
4. Paris-Trousseau/Jacobsen syndrome—cardiac defects, craniofacial anomalies, mental retardation
5. X-linked thrombocytopenia and dyserythropoiesis with or without anemia/X-linked thrombocytopenia α -thalassemia—microcytosis of red blood cells, unbalanced hemoglobin chain synthesis resembling β -thalassemia minor

Pancytopenia

1. Fanconi anemia—short stature, bone marrow failure, renal and skeletal defects and increased risk of malignancy
2. Dyskeratosis congenital—tooth and nail dysplasia, skin rash, bone marrow failure, increased risk of malignancy

Platelet function defects

1. Hermansky-Pudlak syndrome—oculocutaneous albinism, mucosal bleeding
2. Chédiak-Higashi syndrome oculocutaneous albinism, infections, neutrophil peroxidase-positive inclusions
3. MYH9-related disorders cataracts, sensorineural hearing defect, nephritis
4. Leukocyte adhesion deficiency type III recurrent severe infections, delayed separation of the umbilical cord, neutrophilia

Other

1. Fabry disease—typical skin lesions (angiokeratomas), renal and heart disease, typical ocular signs, mucosal bleeding
2. Ehler-Danlos syndrome—skin hyperextensibility, joint laxity present with mucosal bleeding.

APPROACH**History**

A complete history should include age of onset, type of bleeding, sites of bleeding, fate of siblings and any recent illness, surgery or trauma. A past medical history, history suggestive of liver or kidney disease, or malabsorption, should be taken. A medication history should be obtained, with particular attention to anticoagulants,

antiplatelet drugs, NSAIDs, prolonged antibiotic use, and vitamin K and C deficiency. A family history of bleeding disorders may be helpful for assessing pathologic bleeding; probing questions may be needed to elicit a detailed family history.

Examination

Perform a thorough examination to see for petechiae, bruising, and if any cuts or clot are present and if they are still oozing. See

for presence of petechiae (non-blanching hemorrhagic spot < 2 mm diameter), purpura (2–10 mm diameter) or ecchymosis (> 10 mm diameter). Examine for signs of systemic disease—cushingoid features and striae; lymphadenopathy or hepatosplenomegaly; and icterus. Examine joints for prior hemarthrosis or connective tissue disorder. The physical examination should focus on identifying signs of bleeding (e.g., petechiae, mucosal bleeding, soft tissue bleeding, and ecchymoses) as well as signs of systemic disease.

Investigation

A complete history is followed by laboratory evaluation. If there is a suspicion of liver or renal disease, perform liver function and renal function tests. Initial laboratory evaluation for a suspected bleeding or coagulation disorder includes a complete blood count (CBC), prothrombin time (PT), activated partial thromboplastin time (aPTT), and a 1:1 mixing study (**Flow charts 1 and 2**). The 1:1 mixing study helps to identify deficiency or inhibitor of a factor. A bleeding time is useful but needs to be done properly to ensure its validity, platelet function studies should be done after excluding all antiplatelet medications.

SPECIFIC CONDITIONS OF SPECIAL IMPORTANCE

This section has separate chapters on hemophilia, disseminated intravascular coagulopathy (DIC) and ITP.

von Willebrand Disease

If the platelet count and the PT are normal and the aPTT is mildly elevated or normal, then vWD is a likely diagnosis, vWD must be suspected in any patient who has frequent epistaxis, easy bruising or prolonged bleeding from dental surgery. The child may even

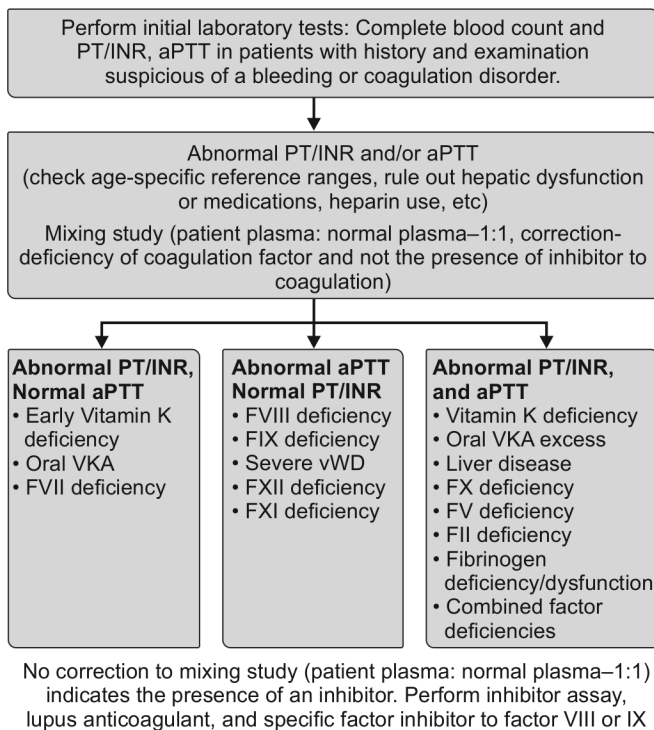
have iron deficiency anemia from chronic blood loss. vWD is the most common inherited bleeding disorder, with an estimated prevalence of 1 in 100. It is inherited as an autosomal dominant disorder, a family history is frequently elicited, however mild cases may go undiagnosed. Diagnosis is based on various tests, including von Willebrand factor (vWF) antigen, vWF activity (ristocetin cofactor or collagen-binding assay), factor VIII assay, and vWF multimers. vWF is a carrier protein for factor VIII in fibrin clot formation. There are three major types. Types 1 and 3 are quantitative deficiencies of vWF, and type 2 defects are qualitative. Laboratory evaluation includes a vWF antigen level, ristocetin cofactor activity (vWF activity level) and factor VIII activity level. All three values are low in type 1 disease and absent in type 3 disease. Type 2 subtype has normal vW antigen levels but low vW and factor VIII activity.

Thrombocytopenia

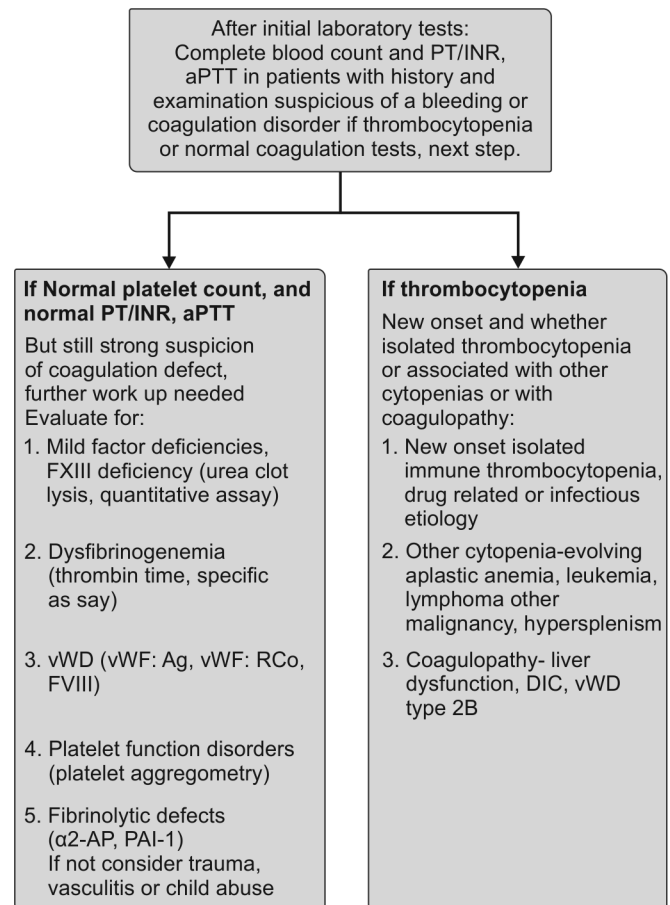
The cause of platelet count reduction in thrombocytopenia depends on the cause. The common causes involve reduced production, increased destruction or sequestration of platelets. Reduced production of platelets like in transient viral suppression of marrow, marrow failure due to acquired aplastic anemia or

Flow chart 2 Approach to a child with bleeding/coagulation disorder; with normal coagulation tests or thrombocytopenia

Flow chart 1 Approach to a child with abnormal coagulation profile



Abbreviations: PT, prothrombin time; INR, international normalized ratio; aPTT, activated partial thromboplastin time.



Abbreviations: PT, prothrombin time; INR, international normalized ratio; aPTT, activated partial thromboplastin time; vWD, von Willebrand disease; vWF, von Willebrand factor.

inherited bone marrow failure syndromes or post-chemotherapy. Increased destruction or loss of platelets occurs in ITP, DIC, sepsis, drug-induced destruction, or dilution in massive transfusion. Sequestration of platelets occurs in conditions of hypersplenism. A bone marrow test may be needed to identify the cause.

Platelet Dysfunction

Common symptoms of platelet function disorders are: frequent nose bleeds, easy bruising, bleeding from the gums. Usually the severe disorders are diagnosed early in life, however, some cases may be milder and present later. Even in the same family symptoms can be very different even among individuals in the same family. Inherited dysfunctions of platelets are recessive rare conditions, usually found in consanguineous families. These include Glanzmann thrombasthenia, Bernard-Soulier and other rare conditions (**Tables 3 and 4**). Here the platelets are normal in number but are abnormal functionally. They require specialized tests to confirm the diagnosis (**Table 5**).

Other Causes of Thrombocytopenia

In pediatric patients with cancer, aplastic anemia or severe sepsis, thrombocytopenia may result from underproduction or excessive consumption of platelets. Studies in adults with normal splenic function indicate that a dose of one single donor apheresis platelet unit/m² (5.5×10^{10} /m²) increases the peripheral platelet count by $10\text{--}12 \times 10^9$ L ($10,000\text{--}12,000/\text{mm}^3$). A rise of less than $5\text{--}6.5 \times 10^9$ L ($< 5,000\text{--}6,500/\text{mm}^3$) for each transfused unit per square meter (i.e., $< 50\%$ of expected) on two consecutive transfusions suggests active destruction resulting from alloimmunization, which can be confirmed with a low post-transfusion platelet count obtained 15–20 min after platelet transfusion and by the presence of antiplatelet

Table 3 Inherited defects with platelet dysfunction and abnormalities of platelet structure or number

<i>Inherited platelet dysfunction, with normal platelet count</i>	<i>Low platelet count and abnormalities in platelets</i>
1. Bernard-Soulier syndrome	1. May-Hegglin anomaly
2. Glanzmann Thrombasthenia	2. Alport syndrome
3. Alpha granule deficiency also called Gray platelet syndrome	3. Wiskott-Aldrich syndrome
4. Dense granule deficiency also called Delta storage pool deficiency	4. vWD type 2B
5. Scott syndrome	

Table 4 Medications and diseases that affect platelet function

<i>Medications- these effects are reversible</i>	<i>Medical conditions</i>
1. Aspirin and other drugs containing aspirin	1. Uremia
2. Nonsteroidal anti-inflammatory drugs like indomethacin, ibuprofen and naproxen	2. Postheart bypass surgery
3. Commonly used drugs can also affect platelet function, e.g., some antibiotics, antihistaminics, etc.	
4. Others clopidogrel, etc.	

Table 5 Evaluation of a child with suspected platelet function defect

<i>Test</i>	<i>Interpretation</i>
Bleeding time	Screening test, difficult in children. If performed needs stringent control. This measures the length of time it takes for a simple cut to stop bleeding
Platelet aggregation studies	Evaluates abnormalities in platelets clumping to different agonists (ADP, adrenaline, collagen, ristocetin, and arachidonic acid)
von Willebrand Factor studies	vWF:Ag, vWF:RCO, FVIII
Specialized tests	Flow cytometry for glycoprotein evaluation, platelet electron microscopy and molecular tests if available

antibodies. Antiplatelet antibodies cause platelet destruction more rapidly than other forms of consumption, and no substantial rise is noted at 15 min after a transfusion.

ACQUIRED DISORDERS OF HEMOSTASIS

Liver Failure and Vitamin K Deficiency

Liver failure causes bleeding through several mechanisms, it results in prolongation of the PT and partial thromboplastin time due to impaired hepatic synthesis or vitamin K deficiency (this decreases factor II, VII, IX and X) (**Box 2**). There is difficulty in correlation of prolongation of PT and aPTT tests, and functional status of the liver. Factor VII has a very short half-life and its deficiency severely influences the PT. Low levels of fibrinogen levels occur in hepatic failure, there may be also be abnormal fibrinogen (dysfibrinogenemia), increased fibrinolysis and thrombocytopenia, dysfunction of platelets is also known to occur.

BOX 2 Etiology of deficiency of vitamin K-dependent factors

- Hemorrhagic disease of the newborn
- Malabsorption of vitamin K (prolonged antibiotic use, short gut, tropical sprue, gluten-induced enteropathy), biliary obstruction
- Vitamin K antagonist therapy (e.g., coumarins, etc.)
- Liver disease
- Disseminated intravascular coagulation.

Uremia

Uremia affects platelet function as do other drugs (**see Table 5**) and causes bleeding by several mechanisms, it is thought that there is dysfunction of GPIIb/IIIa, a platelet membrane glycoprotein which plays a major role in platelet aggregation and adhesion. The other coagulation parameters are generally intact, though platelet count may be slightly reduced, and there is no prolongation of the PT or aPTT. The risk of bleeding is increased and platelet transfusions are needed for major surgery, regular dialysis prior to surgery may improve platelet function. Avoid heparin with the dialysis on the day of surgery.

Disseminated Intravascular Coagulopathy

Disseminated intravascular coagulopathy is an acquired disorder. The presentation range from only an isolated derangement of laboratory parameters to a condition of severe bleeding from multiple sites, associated with high mortality. DIC is triggered by a variety of conditions all of which result in activation of the clotting

BOX 3 What disease states to investigate for in a case of suspected bleeding/coagulation disorder, if baseline tests are normal (normal PT/INR, normal aPTT, normal platelet count)

- All platelet function disorders
- Collagen disorder: Ehler-Danlos, scurvy
- Mild von Willebrand disease
- Factor XIII deficiency
- Mild hemophilia A or B
- α -2-antiplasmin deficiency
- Plasminogen activation inhibitor-1 deficiency

cascade, this leads to deposition of fibrin in the microcirculation resulting in consumption of platelets and clotting factors. As DIC continues, fibrinogen, prothrombin, platelets and other clotting factors are consumed beyond the capacity of the body to compensate and bleeding ensues. Activated protein C has an anti-inflammatory effect and down regulates transcription factor (TF) expression, decreases calcium ion flux. It is consumed in DIC and its supplementation may have an important role in DIC due to sepsis. Antithrombin (AT) is a serine protease inhibitor that can neutralize thrombin and factor Xa, which is also consumed in DIC.

Rare Coagulation Disorders which Cause Clinically Significant Bleeding

Factor X Deficiency

It is an autosomal recessive inherited disorder characterized by severe bleeding episodes. This may also present as a rare acquired condition in patients of amyloidosis, multiple myeloma and other malignancies; *Mycoplasma pneumoniae* infection, and lupus anticoagulant as transient phenomenon and in patients with severe hepatic dysfunction. They present with hematomas, hemarthrosis, and menorrhagia.

Factor XIII Deficiency

It is also a rare (1/1,000,000) autosomal recessive inherited disorder. Even more rarely, an acquired factor XIII deficiency may be seen with Henoch-Schönlein purpura, erosive gastritis, and some leukemias. Patients with factor XIII deficiency will usually have a history of bleeding starting from early childhood, high incidence of intracranial hemorrhage. Hemarthroses are rare, and female patients may have recurrent abortions if they do not receive replacement therapy. The PT, PTT are normal, the diagnosis is made by clot solubility test with 5 M urea and 1% monochloroacetic acid, and confirmed by factor XIII assay.

Congenital Afibrinogenemia

It is a rare (1/1,000,000) autosomal recessive inherited bleeding disorder characterized by the absence of fibrinogen. These patients will have bleeding episodes from early childhood oral, gastrointestinal are common, but can bleed from any site.

CONCLUSION

Occasionally a mild coagulation defects may be missed in early childhood, if the presentation is severe then even if the initial coagulation studies are normal, the child may need further detailed work up as given in **Box 3**. A critically sick, bleeding patient in intensive care may have multifactorial causes for bleeding. Vitamin K deficiency, liver disease and DIC are common causes of bleeding in sick patients, and distinguishing between them is a difficult problem.

IN A NUTSHELL

1. All bleeding children do not have inherited disorders of bleeding or coagulation defects.
2. A detailed history of onset, nature and degree of bleeding is needed.
3. Initial screening tests are complete blood count with platelet count and prothrombin time (PT)/activated partial thromboplastin time (aPTT).
4. Suspect a bleeding or coagulation defect even if initial screening tests are normal, if excessive bleeding, or not controlled by routine measures.
5. Stabilization of child is important, give fluid resuscitation, assess blood volume loss and give blood transfusions if needed.
6. Follow algorithms if screening test are abnormal so that specific diagnostic tests can be performed with less cost and in a timely manner.
7. Consider acquired causes of bleeding in a sick child, in very ill children bleeding may be multifactorial.

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Chapter 38.17

Hemophilia

Pravas Mishra

Hemophilia is congenital X-linked disorder of the coagulation system whereby deficiency of factor VIII (hemophilia A) or factor IX (hemophilia B) predisposes the affected male to a lifelong risk of bleeds. Descriptions of hemophilia are among the earliest known accounts of genetic disease. Jewish texts in 5th century and Arab physicians in the 12th century AD have described it. In its severe form, it primarily involves the joints but could also result in fatal bleeds involving organs such as the central nervous system or the gastrointestinal tract. Early and adequate support with factor replacement will prevent death from fatal bleeds. Factor replacement along with physiotherapy will ensure that debilitating joint deformities are avoided as also fatal bleeds. This is not an uncommon deficiency. However awareness levels among students and general practitioners continue to be very low resulting in inappropriate therapeutic interventions including potentially surgical interventions. This chapter will focus on the presentation, genetic aspects, prophylactic therapy and management of bleeds including factor support during surgery.

EPIDEMIOLOGY

The inheritance of hemophilia is X-linked, with an overall incidence of about 1:5,000 males for hemophilia A and 1:30,000 males for hemophilia B. Prevalence data of hemophilia A varies from 2.26 per 100,000 males in India to 20.6 per 100,000 males in the U.S. Corresponding figures for hemophilia B are 0.6 and 5.3 respectively. The Indian data reflects the poor awareness of the disease at the primary care level resulting in underreporting rather than a real prevalence. As per data from the Hemophilia Federation of India (HFI), there are 19,000 patients registered in the 70 HFI chapters all over India. There are 2,500 patients in the Delhi and surrounding regions. As per internationally published incidence and prevalence in various countries, including other Asian countries, as per estimates 1,90,000 patients should be in India.

ETIOLOGY

Hemophilia is a genetic disorder. The gene loci for factors VIII and factor IX exist on the long arm of the X chromosome (Xq28 and Xq27 respectively). Thus hemophilia is an X-linked disorder that is transmitted to 50% of children of a carrier mother, 50% of daughters will be carriers and 50% sons will be hemophiliac. It is transmitted as a carrier state to all female children of an affected male and to none of his male offspring, who get their normal X chromosome from the mother. Besides this mode of transmission, there is an approximately 30% chance of developing a new mutation resulting in a male hemophiliac or a female carrier with no family history of bleeding. This is more likely for factor VIII, which has a large and complex gene structure compared to factor IX. Indeed a positive family history is absent in nearly half of patients. There is no known environmental trigger for a spontaneous mutation. A family history is useful if present, in determining the presence of a suspected hemophiliac. The converse is not true, as in addition to chances of spontaneous mutation; the gene could have been transmitted through female carriers alone. A female hemophiliac is possible in the rare events as in cases of lyonization whereby the normal X chromosome is inactivated or in cases of Turner's syndrome. Homozygous transmission (affected father and carrier mother) has also been rarely described resulting in classical hemophilia

presentation in females. However a diagnosis of hemophilia must not form the primary differential in a female bleeder where von Willebrand factor (vWF) deficiency is a more likely cause of a prolonged activated partial thromboplastin time (APTT) with normal prothrombin time (PT).

PATHOPHYSIOLOGY

Factors VIII and IX are components of the *intrinsic system* of the coagulation cascade. The classical extrinsic and intrinsic systems are closely intertwined in the human body. The coagulation pathway is initiated after vessel wall injury whereby exposed tissue factor (TF) and activated factor VII (VIIa) combine to activate factor X and factor V. The activated factor X-factor V combination is called the *prothrombinase complex*. This leads to a small clot following thrombin generation, which is insufficient for maintaining homeostasis. This small quantity of thrombin activates factor VIII and factor IX, which together form the *tenase complex*, so named because it activates factor X. The tenase complex is a far more potent activator of the factor X compared to the TF-VIIa complex and generates greater amounts of the prothrombinase complex ultimately producing sufficient quantities of thrombin to form a stable and effective clot. Thus both these factors, VIII and IX, form important components of a positive feedback loop system and deficiencies of factor VIII (hemophilia A) and factor IX (hemophilia B) result in the classical bleeding manifestations of hemophilia. Patients with mild (factor level > 5% of normal) or moderate hemophilia (factor levels between 1% and 5%) generally bleed only after trauma. Experimental models have demonstrated that complete absence of coagulation factors such as factors VII, X, V, prothrombin and TF is incompatible with life whereas null alleles for factors VIII and IX result in the spontaneous bleeds characteristic of patients with severe hemophilia (factor levels < 1% of normal).

PATHOGENESIS OF JOINT DAMAGE

A young male with deformed swollen joints, with restricted range of movements, often unable to walk without support is the classical picture of severe hemophilia. The reason for predilection of joints to bleed is not entirely clear. The large joints are routinely exposed to mechanical stresses. In addition the joint capsule has been found to be deficient in thromboplastic activity. The synovium also synthesizes TF pathway inhibitor which has anti-Xa activity. This perhaps makes it more likely for joints to bleed more readily.

In the initial phases, hemorrhage occurs into the synovial cavity or into the diaphysis or epiphysis of bone. The muscles surrounding the affected area go into a painful spasm. Without further bleed, the blood gets broken down and is removed by the subsynovial venous plexus over 3–4 weeks. The joint regains its normal shape and functions normally following the initial bleeds. At this point the joint retains its full range of motion and the only evidence of an affected joint on clinical examination could be the presence of crepitus on movement of the affected joint. Repeated bleeds into the joint overcomes the capacity of the synovium to remove the accumulated blood and finally it gets permanently swollen. The swollen joint may be painful with restricted range of movement. This swelling is because of synovial hypertrophy. The synovium gets chronically inflamed because of the retained blood products which break down to release iron, which in turn stimulates inflammatory cytokines which further damage the cartilage and bone. These cytokines induced c-myc and mdm2 oncogenes which stimulate synovial proliferation. Successive bleeds result in a thickened, irregular synovium with folds and friable outcrops, which are extremely vascular. These folds get caught between the joint surfaces and cause further bleeds. Progressive damage to synovium and

cartilage is followed by development of subchondral cysts in the initial stages. Joint damage in hemophilia progresses through five stages (**Table 1**). In the final stages, loss of hyaline cartilage at the joint margins, subchondral hemorrhages, diffuse demineralization of affected bone occur, ultimately leading to ankylosed bone which may manifest as a fixed flexion deformity. Permanent joint damage starts to set in after 3–6 consecutive bleeds.

CLINICAL PRESENTATION

Hemophilia A is 4–6 times commoner than hemophilia B. This ratio has varied from 4.2:1 to 6.4:1 in Indian studies. The presentation of both hemophilia A and B are the same. The median age at diagnosis in western data is 8 months for severe and 12 months for moderate hemophilia A and B. Nearly half of patients in India had history of bleed by the age of 1 year. As seen from **Figures 1 to 4**, the frequency of symptoms reduces with increasing factor levels. Joint bleeds predominate in the severe hemophilia group. Skin bleeds and other superficial bleeds following trauma predominate as presenting complaints in children below 2 years, whereas joint bleeds without any history of trauma are the primary problem as the child grows. The earliest superficial skin bleeds in the form of spontaneous ecchymosis patches and easy bruising appear by age of 1 month and peaks by 1 year of age. Thereafter dental issues lead to mucosal bleeds in the form of spontaneous gum or dental bleed. Joint swellings start appearing by the age of 1 year. This is also the time traumatic bleeds predominate. After the age of 10 years, joint bleeds are the major cause of bleed. Absence of umbilical bleed at birth or bleed following circumcision does not rule out hemophilia. Post-circumcision bleed has been described in less than half of severe hemophiliacs.

Pattern of Musculoskeletal Bleeds

The knee is most commonly involved (40–50%), followed by the elbow (30–35%), ankle (20–30%), shoulder and hip (5–15%) and wrist in nearly 20% of patients. In the absence of swelling and inability to describe their problem, small children present with irritability and guarding of the affected joint. Intramuscular bleed has been reported in 30% of severe hemophiliacs, predominantly iliopsoas bleeds, followed by the thigh and calf muscles. Chronic hemophilic arthropathy in untreated individuals would present with muscle atrophy and weakness around the joint which predisposes to further bleeds. Joint appear swollen and often have fixed flexion and valgus deformities (**Fig. 5**). Bleed in the forearm could result in compartment syndrome if left untreated. It has been seen commonly after injections or attempts at phlebotomy in the antecubital fossa.

Pseudotumors

They are infrequent complications in western patients on account of prophylactic therapy. These are essentially collections of blood surrounded by a *capsule* of surrounding structures, either soft tissue or muscle or bone (**Fig. 6**). Pseudotumors in bony structures result from subperiosteal bleeding which separates the periosteum

Table 1 The five stages of joint damage in hemophilia

Stage 1	Intraarticular and periarticular swelling due to acute bleed
Stage 2	Loss of bone density around the joint and epiphyseal hypertrophy secondary to chronic synovial hypertrophy
Stage 3	Progression of epiphyseal hypertrophy with widening of intercondylar notch
Stage 4	Articular cartilage surfaces affected
Stage 5	Advanced cartilage erosion, loss of joint space, joint fusion and fibrosis

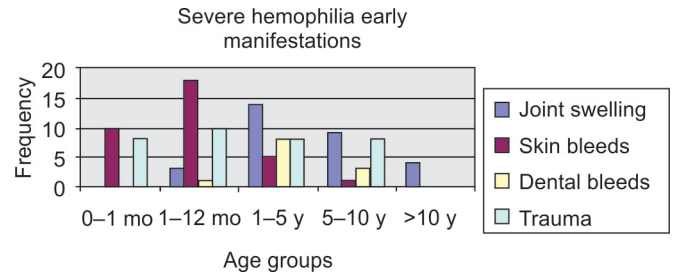


Figure 1 Bleeding manifestations of severe hemophilia

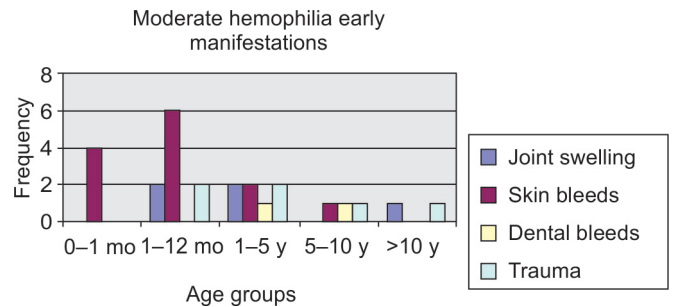


Figure 2 Bleeding manifestations of moderate hemophilia

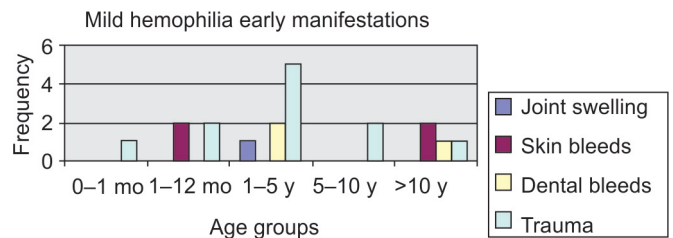


Figure 3 Bleeding manifestations of mild hemophilia

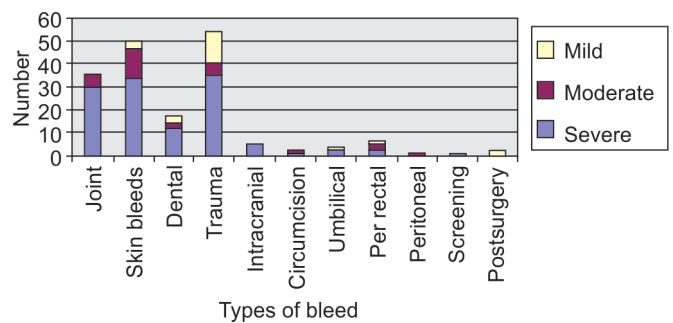


Figure 4 Bleeding episodes leading to a diagnosis of hemophilia

from the underlying bone. Subsequent bleeds into the cyst result in an expansile lesion which erodes surrounding structures like a tumor. Some of these lesions develop sinus tracts which keep on oozing and get chronically infected. These masses usually develop in the lower limbs and pelvis but are known to occur in the small bones of the hands and feet in children.

Other Severe Bleeds

Intracranial bleed is life threatening and has been observed in less than 5% of cases. Uncomplicated vaginal deliveries pose a small risk for intracranial bleed (< 3.8%) and cesarian section does not completely eliminate the risk. However application of forceps or vacuum extraction and prolonged labor increases the risk of



Figure 5 Hemophilic joints



Figure 6 Hemophilic pseudotumor with secondary calcification

intracranial bleeds. Prior to effective factor replacement therapy, the mortality rate for this complication was as high as 70% (in the 1960s), reduced to 25–35% after introduction of factor concentrate therapy. In studies where detailed psychomotor analyses in the form of EEGs combined with psychiatric assessment were done, the incidence of neurological deficits was as high as 75%. However, only 3–10% of intracranial bleed survivors with such deficits had severe malfunctions. Gastrointestinal bleed occurs in nearly 10% of cases while 5% of children may present with urinary bleed.

INVESTIGATIONS

A prolonged APTT could mean any of the following deficiencies: factor VIII, factor IX, factor XI and factor XII. von Willebrand and factor deficiency could also result in a prolonged APTT owing to low levels of factor VIII. The first step would be to do a mixing study with normal plasma in a 50:50 mixture. In case of a factor deficiency, the prolonged APTT would be corrected but it would remain prolonged in case of an inhibitor such as lupus or other acquired inhibitor. If the mixing study demonstrates a correction of APTT, then specific factor assays would need to be performed

to determine the exact deficiency. These tests are bioassays, which determine the factor activity levels of the deficient factor (factor VIIIc or factor IXc) rather than actual factor antigen levels (VIII Ag or IX Ag). There is good correlation between factor antigen levels as determined by immunoradiometric methods and enzyme-linked immunoassay techniques.

As an example a bioassay for factor VIII requires three samples: the test sample, a standard reference sample (this contains 100% of all factors) and a substrate sample (a sample with known deficiency of factor VIII). APTT is performed on serial dilutions of the standard and test samples mixed with equal volumes of the substrate. The APTT values obtained are plotted on semi log paper and factor levels in the test sample determined from this log paper. As the substrate sample has normal levels of all factors other than factor VIII, APTT of the test sample would overlap with the standard sample if there were no deficiency of factor VIII. In such a case the test would have to be repeated using a factor IX deficient substrate. Bioassays for all factor deficiencies follow the same principle as described here for factor VIII.

In the event of factor VIII or IX deficiency the test results are reported in terms of factor activity percentage. Factor levels less than 1% are considered severe, 1–5% as moderate and levels greater than 5% but less than 30% are considered mild deficiencies. It is essential that the following precautions be taken for coagulation studies. The sample is preferably drawn from a clean venipuncture site avoiding indwelling heparinized catheters. The sample is collected into a citrate tube with 3.2% trisodium citrate concentration. The volume of blood as specified by markings on the tube has to be adhered to. This corresponds to a 9:1 dilution of blood to citrate. The sample tube, ideally collected near the laboratory, is to be transported at 15–22°C. Temperatures more than 22°C and less than 8°C could activate clotting factors. Samples to evaluate efficacy of factor therapy have to be drawn within 15 min of administration of factor. The platelet poor plasma is separated by centrifuge within 1 hour of drawing the sample. This can then be evaluated within 4 hours. If this is not possible, then a platelet poor plasma sample can be stored at –30°C for 4 weeks and –70°C for 6 months.

MANAGEMENT

General Care of a Hemophilic Child

The patient and his family must be educated about the disease and when to seek medical care. A detailed description of diagnosis and possible factor replacement products along with emergency contact numbers must be given to the patient. The mother must be counseled about prenatal diagnosis for future pregnancies. Intramuscular injections are contraindicated and injections should be given intravenously or subcutaneously. These children should receive all recommended immunization. The injection should only be given subcutaneously using a 26-gauge needle and pressure applied for 2–3 min. Infants should be allowed soft toys and must not be left unattended in raised seats or beds. Furniture in rooms should be minimum and should not be sharp edged. As the child grows and becomes mobile, he is at risk of injuries and joint bleeds. Ideally a severe hemophilic should be on factor prophylaxis. The aim of factor prophylaxis is to provide normal life as any other child. The child on prophylaxis should be encouraged to take part in routine physical exercises. He must avoid contact sports with significant risk of trauma such as football, cricket and high impact activities such as jumping on a trampoline. Sports such as badminton, swimming, cycling is considered safe. The child must wear protective gear such as helmets, knee and elbow pads while cycling. Martial arts (without physical contact) and dance are also considered safe but in general any activity, which involves possibility of high impact, sudden or jerky movements,

must be avoided. Blood clotting agents such as tranexamic acid are contraindicated in presence of urinary bleeds to avoid clot colic. The child must avoid nonsteroidal anti-inflammatory agents.

First Aid

In case of a joint or limb bleed, the patient is advised RICE (**R**est, **I**ce, **I**mmobilization, **C**ompression, and **E**levation) therapy (**Table 2**). RICE therapy has to be accompanied by factor replacement for successful management of the bleed.

Factor Replacement Therapy: Basic Considerations

Table 3 describes the recommended factor levels for acute bleeds including factor support during acute bleeds and surgical procedures. The hemostatic levels or the approximate blood levels of the deficient factor required to control bleeding episode has been empirically determined. It is 25–30 IU/dL for factor VIII and 15–30 IU/dL for factor IX. An example of factor correction is as follows: a 100% correction in a 30 kg child with severe hemophilia requires 3,000 units of factor (30×100). In case of hemophilia A, each unit of factor VIII raises the factor levels to 0.02 U/mL.

Table 2 RICE (Rest, Ice, Immobilization, Compress, Elevation) therapy

<i>Rest</i>	The joint should be rested till it heals. If knee or ankle is involved then walking must not be allowed
<i>Ice</i>	Use crushed ice wrapped in a damp towel for 10–15 min at a time. Ice baths are useful for ankle, wrist or hand involvement
<i>Immobilization</i>	A half cast or splint is used to limit movement
<i>Compress</i>	Wrap the foot or muscle starting well below the affected area and ending well above the affected area, using crisscross pattern
<i>Elevation</i>	Elevate the affected limb above the level of the heart using cushions

Therefore the required dose would be 1,500 units. However as the median half-life of factor VIII is 12 hours, another dose of 750 units is required after 12 hours to maintain 100% factor levels.

In case of hemophilia B, each unit of factor IX raises the levels to 0.01 U/mL and the median half-life of factor IX is 24 hours. A single dose of 3,000 units is required in this case, administered once every 24 hours, to maintain 100% factor levels. If factor concentrates were required on subsequent days as for a major bleed or surgery, one would need to make allowance for residual factor activity from the previous day's administration. Duration of therapy and factor level required to control various bleeds are given in **Table 3**. **Table 4** provides a guideline to administer factor concentrate so as to achieve the recommended factor levels in patients undergoing major surgery. It is necessary to monitor factor levels daily for the first 3–4 days followed by a reduced frequency of testing. This would ensure target levels are maintained. This also ensures that over dosage and wastage of factor is avoided.

Physiotherapy and Rehabilitation

Physiotherapy is a useful and necessary adjunct to prophylactic therapy, with the likelihood of reducing the dependence of factor requirement. Physiotherapy forms an important part of a comprehensive hemophilia treatment center, which would have orthopedicians, physiotherapists, and nurses in addition to hematologists. Effective physiotherapy increases the muscular strength. Physiotherapy should be initiated as quickly as feasible to avoid weakness in the other joints that would compensate for loss of activity in the affected joint. An exercise regimen would aim to restore range of movement, muscle strength and proprioception, at least to the degree that existed prior to the bleed. These regimens typically put the patient gradually through different levels of difficulty. An example of an exercise regimen for a hemophilic knee is given in **Table 5**. Level 1 exercise could start after the bleeding subsides. Even if no factor is available a patient could be encouraged to take up a level 1 exercise and gradually go to

Table 3 Suggested correction of factor deficiency in hemophilia as per indication

Type of bleed	Hemophilia A		Hemophilia B	
	Desired level (%)	Duration (days): adjusted as per response	Desired level (%)	Duration (days): adjusted as per response
Joint	10–20	1–2 days	10–20	1–2 days
Superficial muscle/no neurovascular compromise	10–20	2–3 days	10–20	2–3 days
Iliopsoas muscle				
Initial	20–40	1–2	15–30	1–2
Maintenance	10–20	3–5	10–20	3–5
CNS				
Initial	50–80	1–3	50–80	1–3
Maintenance	30–50	4–7	30–50	4–7
	20–40	8–14	20–40	8–14
Gastrointestinal				
Initial	30–50	1–3	30–50	1–3
Maintenance	10–20	4–7	10–20	4–7
Urinary tract	20–40	3–5 days	20–40	3–5 days
Major surgery	CNS, Intra-abdominal, Orthopedic, Intrathoracic			
	60–80	Preoperative	50–70	Preoperative
	30–40	1–3	30–40	1–3
	20–30	4–6	20–30	4–6
	10–20	7–14	10–20	7–14
Minor surgery	Including tooth extraction			
	40–80	Preoperative	40–80	Preoperative
	20–50	1–5	20–50	1–5

(Adapted with permission from World Federation of Hemophilia guidelines for the management of hemophilia where there is significant resource constraint. Hemophilia. 2013;19:e1–47)

Table 4 Guidelines to administer factors during major surgery

Day	Bolus dosing (IU/kg)		Interval frequency in hours	
	VIII	IX	VIII	IX
Preoperative	40–50	60–70	Preoperative	Preoperative
1–3	20–25	40–60	12	24
4+	15–20	20–40	12	24

the next level if there is no discomfort. At the same time one must take care of the following points:

- Patient comfort is of paramount importance and no patient must be asked to continue exercise in case of discomfort.
- One would need to tailor a target level of movement as per the patient's requirement.
- Each level of exercise has to be crossed gradually and the next level started only if there is no discomfort with the previous level.
- Isometric exercises where a patient contracts groups of muscles without joint movement are useful in case any form of discomfort arises from joint motion.

Prevention of Bleeding Episodes

Most moderate and mild hemophiliacs do not have spontaneous bleed and therefore do not require replacement therapy. However severe hemophiliacs have lifetime risk of fatal bleeds and joint bleeds. Replacement therapy is called *prophylaxis* when factor concentrate is given at regular intervals in the absence of bleed and it is called *episodic* or on demand when given only when a bleed occurs.

Prophylaxis is primary where factor replacement therapy is started after first large joint bleed (ankles, knees, hips, elbows, shoulders) before age of 2 years. There should not be any clinical or radiological evidence of joint damage. Prophylaxis is secondary when one waits for two major joint bleeds but no joint involvement, clinically or radiologically. Tertiary prophylaxis starts after the onset

of joint damage. The world federation of hemophilia further defines prophylaxis as continuous where prophylactic therapy is provided for at least 45 weeks/year and intermittent if less than 45 weeks. It is not necessary to maintain trough levels of factor more than 1% for efficacy. Prophylaxis for hemophilia A is traditionally given thrice a week and twice in case of hemophilia B. The various dosing regimens in use are enumerated in **Table 6**. The Malmo protocol is associated with least bleeds but results in high factor requirements; on average about 6,000 IU/kg/year/person. The Utrecht protocol uses 2,100 IU/kg/person/year at the cost of 1.3 bleeds every year and somewhat more joint damage as compared to Swedish patients on the Malmo protocol. A Chinese study attempted very low doses of factor VIII at 20 IU/kg/dose/week. However the patients in this study suffered 12–15 joint bleeds every year the Canadian protocol recommends factor replacement to patients on once weekly dosing.

Treatment of Minor Bleeding Episodes

Vasopressin (DDAVP) is an alternative to plasma or factor concentrate administration in case of minor bleeds or minor surgical procedures in mild hemophiliacs. Vasopressin acts on vascular endothelial cells to release high molecular weight multimers of vWF (and thereby factor VIII which is bound to vWF) to 2–5 times normal levels. Thus it is most useful in patients with factor levels more than 5%. The vWF so released increases platelet adhesion and function at sites of tissue injury. Repeated use of DDAVP results in diminishing effect (tachyphylaxis). DDAVP is administered intravenously at a dose of 0.3 mcg/kg up to a maximum of 24 mcg/kg/day. It is also available as a nasal spray. The DDAVP nasal spray for hemophilia supplies 150 mcg/metered dose. Other useful adjuncts are epsilon aminocaproic acid (EACA) administered orally or intravenously every 4–6 hours to total dose not exceeding 24 g/day or tranexamic acid (25 mg/kg orally every 6–8 hours). These could be used for minor bleeds but are of limited benefit in prevention or treatment of major bleeds. Both EACA and tranexamic acid are contraindicated for use in hematuria as blood clots could cause ureteric obstruction.

Table 5 Rehabilitation regimen for hemophilic knee

Levels of exercise	Range of motion	Strength	Proprioception
1	Sitting with legs out straight, bend hip and knee, slide heel towards body. Then straighten knee by sliding heel away from body. Repeat several times	Lie on back with roll under knee. Extend the knee and lift heel. Hold and relax. Repeat several times	Stand on affected leg. Maintain balance as long as possible
2	Sit on a chair. Bend knee as much as comfortable then extend knee	Sit on chair. Extend knee and lift foot off ground. Keep up as long as possible	Do level 1 with eyes closed as long as possible
3	Lie on stomach and bend knee to touch heel to buttock, then straighten out	Sit on chair. Cross ankles together and press them towards each other keeping them so as long as possible	Do level 1 on an uneven surface like pillow
4		Lie on back with roll under knee. Do level 1 with weights on ankle	Do level 3 with eyes closed
5		Stand on both feet and squat down as much as comfortable. Hold for few seconds then straighten up	Jump off a step (10–15 cm) and keep balance on standing. To be attempted only if knee or ankle are not swollen
6		Stand with back to wall. Slide down the wall till comfortable and then slide back up after few seconds	
7		Step up with affected leg onto a step	
8		Stand on a step and step down using the better leg	
9		Stand up from kneeling posture using affected foot	

The patient should go to the next level only if there is no pain on the previous level.

(Adapted with permission from Mulder K. Exercises for children with hemophilia. Montreal: World Federation of Hemophilia 2006)

Table 6 Prophylaxis regimens for hemophilia

Protocol	Dosing schedule	Time to start
Malmo (Sweden)	25–40 IU/kg thrice weekly for factor VIII, twice weekly for factor IX	Age < 2 years before any joint bleed
Utrecht	15–25 IU/kg thrice weekly for factor VIII, twice weekly for factor IX	After 1–2 joint bleeds
Canadian	50 IU/kg/dose weekly; option to increase dose and frequency as per bleed	Before 2 years of age; before any joint bleed

Novel Therapies

Gene therapy for hemophilia could potentially free the patients from need for regular intravenous injections for replacement therapy. A recent study demonstrated some success in maintaining factor IX expression in humans using adeno-associated virus (AAV) vector. This approach is under clinical trials but is limited by the fact that 40% males would have antibodies to AAV due to prior exposure. Factor VIII molecule is too large to be packaged into conventional AAV vector. Recombinant retroviruses were studied initially but there is risk of insertional mutagenesis. This is less with self-inactivating lentiviral vector which have been used to transduce hematopoietic stem cells without risk of mutagenesis. Lentiviruses are not yet approved for clinical trials.

Inhibitors

Patients with hemophilia sometimes develop inhibitors to the deficient factor. These are alloantibodies directed against the deficient factor, more often factor VIII and result from the administration of exogenous factor. Patients who develop inhibitors no longer respond to pharmacological doses of factor concentrate therapy. Bleeds in these patients would require large doses of factor concentrate if the inhibitor titer is low. In most cases where the inhibitor titer is high, the factor bypassing agents such as factor eight inhibitor bypassing agent (FEIBA) or recombinant factor VII are required to stop the bleed. The overall incidence of inhibitors worldwide is 30% of all severe Hemophiliacs and that of persistent clinically significant inhibitors (> 10 BU/mL) is 10–20%.

Genetic predisposition plays a large role in inhibitor formation. Patients with large deletions (inversions of intron 22, intron 1, large deletions, nonsense mutations and missense mutations) are more likely to develop inhibitors. These are patients who have very little factor and thus would develop antibodies more readily on exposure to exogenous factor. Intron 22 inversion is seen in 35–42% patients with severe hemophilia. The proportion is roughly the same in Indian and western literature.

PREVENTION OF HEMOPHILIA

Birth of hemophilic child can be prevented by aborting the affected fetuses (if acceptable to the parents). One would continue to have

sporadic cases of hemophilia in families. However a positive family history provides an opportunity to prevent further hemophilic births by first identifying carriers and then affected fetuses. This is possible through prenatal counseling and testing of the mother for carrier status and the male fetus for hemophilia. Carrier status is important to plan future pregnancies and to decide continuation of a present pregnancy. Carriers could be obligate or possible (Table 7). Suspected carriers can be screened by coagulation and DNA based assays. A family history and a reduced ratio of factor VIIIc to vWF are associated with an increased probability of being a carrier. However this is not as reliable as DNA based tests. Direct DNA mutation analysis of the gene amplified by polymerase chain reaction is the most accurate method. Linkage analysis is another method using restricted fragment length polymorphism (RFLP) techniques where direct mutation analysis is not available. Linkage analysis looks for genes, which are known to co-segregate with the affected gene. These are present in affected family members and absent in the others. Thus indirect information about the carrier status can be obtained without knowing the actual mutation. Combination of single nucleotide polymorphisms such as xba1 and bcl1, variable number of tandem repeats (VNTR) in introns 13 and 22 (CA-13, CA-22) and direct mutation analysis of inversions in introns 22 and 1 provided informative data in 85% of cases with a family history and 52% of sporadic cases of hemophilia A. The intron 22 inversion is common and accounts for over 40% of severe hemophiliacs. This combination of markers could vary in different populations. Combination of these tests could be undertaken in the family and on chorionic villus sample to identify the affected fetus, followed by counseling and termination of pregnancy, if needed.

IN A NUTSHELL

1. Hemophilia is a genetic X-linked disorder, transmitted to males via female carrier.
2. It primarily affects the joints but manifests in the early age as easy bruising and mucosal bleeds.
3. The management of an acute bleed not only involves the use of factor but also appropriate first aid using RICE therapy and physiotherapy.
4. The factor support is complemented with physiotherapy and joint rehabilitation techniques in consultation with the physiotherapist.
5. Factor concentrate prophylaxis has to start early (as soon as possible after first bleed if not earlier) to avoid permanent irreversible joint damage.
6. Prophylaxis therapy is preferred to on demand factor support, as the latter does not prevent joint damage.
7. Several factor concentrates are available of which factors produced by recombinant techniques are preferred over plasma-derived concentrates owing to perceived lower risk of transmitting infection.
8. Prevention of hemophilic births depends on prenatal diagnosis using molecular techniques in pregnant carriers.

Table 7 Carrier determination in hemophilia

Obligate carriers	Possible carriers
1. All daughters of a father with hemophilia;	1. All daughters of a carrier;
2. Mothers of one son with hemophilia and who have at least one other family member with hemophilia (a brother, maternal grandfather, uncle, nephew, or cousin);	2. Mothers of one son with hemophilia but who do not have any other family members who have hemophilia (or are carriers);
3. Mothers of one son with hemophilia and who have a family member who is a known carrier of the hemophilia gene (a mother, sister, maternal grandmother, aunt, niece, or cousin);	3. Sisters, mothers, maternal grandmothers, aunts, nieces, and female cousins of carriers.
4. Mothers of two or more sons with hemophilia.	

Reproduced with permission. Carriers and women with hemophilia. Montreal: World Federation of Hemophilia 2012

MORE ON THIS TOPIC

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Chapter 38.18

Other Clotting Factor Deficiencies

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Common coagulation abnormalities include deficiency of factor VIII and factor IX. These have been discussed earlier. Other clotting factor deficiencies are rare and their diagnosis thus is suspected only on high index of suspicion. This chapter will primarily discuss deficiencies of factors V, VII, X, and XIII.

EPIDEMIOLOGY

Among 600 children with coagulation disorder, hemophilia A was most common coagulation disorder (70.80%), followed by von Willebrand disease (vWD) (14.1%), and hemophilia B (8.4%). Other deficiencies noticed were factor V, factor IX and factor XII deficiencies which were rare.

Deficiency of vitamin K causes hemorrhagic disease of newborn (HDN), which may present with mild-to-severe disease. Many of these newborns may have vitamin K deficiency which goes undetected or asymptomatic. So, predicting its incidence is equivalent to tip of an iceberg. The incidence of the disease shows widely variable figures ranging from 4 to 170 per 100,000 births. Review of number of studies of Europe and Asia showed incidence of late HDN as 4.4–7.2 per 100,000 births in vitamin K unsupplemented groups. The incidence in vitamin K supplemented groups was 1.4–6.4 per 100,000 births. The von Willebrand disease is seen in about 10% of cases with hereditary bleeding disorder. The common subtypes are type 1, type 2a, type 2b and type 3 vWD.

The prevalence of factor XIII deficiency in general population is 1 in 200,000 births. It is a rare coagulation disorder. Its prevalence is higher in countries with consanguinity. The prevalence of inherited coagulation factor disorders is shown in **Table 1**.

LABORATORY EVALUATION

Once a coagulation disorder is suspected, laboratory evaluation is done to confirm the diagnosis. The laboratory tests include screening tests and confirmatory tests.

Screening Tests

These include bleeding time (BT), platelet count, platelet function tests, prothrombin time (PT) and acquired partial thromboplastin time (aPTT). PT tests the efficiency of extrinsic pathway and common pathway. It uses calcium and tissue thromboplastin for the formation of thrombin. Normal PT: 10–12 s (11–16 s). Causes of prolonged PT are deficiency of factor II, V, VII, X; vitamin K deficiency; acquired causes: disseminated intravascular coagulation (DIC), liver disease, oral anticoagulants intake. aPTT assesses the intrinsic pathway. This test depends on contact factor, prothrombin, fibrinogen, factor VIII, factor IX, X, and V. Normal aPTT: 25–35 s. Difference between test and control should be less than 6 s. If it is more than 10 s, it is abnormal. Causes of prolonged aPTT are deficiency of factor VIII, IX, X and factors of intrinsic pathway, vitamin K deficiency, liver disease, DIC, massive transfusion with stored blood, heparin, and oral anticoagulants.

Confirmatory Coagulation Tests

Thrombin Time

It is the time taken for formation of fibrinogen to fibrin induced by thrombin. It is prolonged when the levels of fibrinogen are reduced or absent or there is presence of fibrin degradation products. Dysfibrinogenemias can be diagnosed by this test. Normal thrombin time (TT): within 2 seconds of control, >24 seconds is abnormal.

Mixing Studies

Mixing studies also called as correction studies are done to define abnormality once the initial screening tests like PT, partial thromboplastin time with kaolin (PTTK) are prolonged. These tests are done to identify the specific abnormality. Mixing studies are also helpful in differentiating the factor deficiency from circulating inhibitor.

Table 1 Prevalence of inherited coagulation disorders

Factor deficiency	Genetics	Prevalence	BT	APTT	PT
Afibrinogenemia	AR	1:1 million	N	P	P
Dysfibrinogenemia	AR		N	N/P	P
II	AR	1:2 million	N	P	P
V (Parahemophilia)	AR	1:1 million	N	P	P
VII	AR	1:500,000	N	N	P
VIII (Hemophilia A)	XLR	1:10,000	N	P	N
von Willebrand disease	AD	1:1,000	N/P	N/P	N
IX (Hemophilia B)	XLR	1:60,000	N	P	N
X	AR	1:1 million	N	P	P
XI (Hemophilia C)	AR	1:1 million	N	P	N
XII	AD		N	P	N
XIII	AR	1:1 million	N	N	N
Prekallikrein	AD		N	P	N
HMW kininogen	AR		N	P	N

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; XLR, X-linked recessive; APTT, activated partial thromboplastin time; BT, bleeding time; PT, prothrombin time; N, normal; P, prolonged

Principle Mixing studies are used to evaluate prolonged aPTT or PT. Patient plasma is mixed with equal amount of normal plasma. Correction of initial screening test such PTT immediately indicates factor deficiency. If it does not get corrected, circulating inhibitor is suspected. Various incubation times like 30, 60, 120 minutes are used. Various plasmas which are used are normal plasma, aged plasma, and adsorbed plasma.

Aged plasma is deficient in factors I, V and VIII and contains II, VII, IX, X, XI, XII. Adsorbed plasma contains I, V, VIII, XI, XII. Plasma from patients with isolated severe deficiency (<1 IU/dL) of FVIII or FIX are very useful for mixing studies. The interpretation of mixing studies is given in **Tables 2A and B**.

Diagnosis of factor VIII inhibitors In presence of factor VIII inhibitor, aPTT initially normalizes by mixing studies but again gets prolonged after 1–2 hours of incubation. History of previous bleeding episodes is asked. Sometime factor VIII inhibitor can develop transiently after pregnancy and surgery with no prior history of bleeding. Confirmation is done by Bethesda titer.

Clotting Factor Activity Assays

The amount of clotting factors normally in plasma varies from 50% to 150%. The factor assays are used to differentiate and identify the deficient clotting factor. The severity of disorder is assessed by the amount of factor.

Severe deficiency	<1% of normal plasma
Moderate deficiency	1–5% of normal plasma
Mild deficiency	>5% of normal plasma

The von Willebrand Factor (Ristocetin Cofactor Activity)

It is the functional assay for von Willebrand factor. It is performed when vWD is suspected, BT is prolonged, or platelet function test is abnormal.

Urea Clot Lysis Test

It is used to assess factor XIII deficiency. Normally, clot is formed by conversion of fibrin to cross-linked fibrin in presence of activated factor XIII. This clot is stable for at least 1 hour in monochloroacetic acid solution or 5 molar urea. In absence of factor XIII, clot dissolves rapidly when incubated with 5 molar urea.

A diagnosis can be arrived at by a stepwise approach to history, physical examination, and screening test. Finally, minimum test is

applied to reach to a definitive diagnosis. This approach is cost-effective and minimizes the possibility of misdiagnosis and missed diagnosis. Common scenarios are summarized in **Table 3**.

VITAMIN K DEFICIENCY BLEEDING DISORDER

Pathogenesis

Vitamin K is a group of compounds that have a common naphthoquinone ring structure. Three type of vitamin K are seen. Vitamin K₁ or *phylloquinone* is present in dietary sources like green leafy vegetables, vegetable oils, etc. It is used for food fortification. This form of vitamin is given prophylactically to neonates as aqueous and colloidal solution. Vitamin K₂ or menaquinones are produced by gut flora, also present in meat, liver, and cheese. Vitamin K₃ or *menadione* is a synthetic form of vitamin K and is not used medically because it can cause hemolytic anemia. Vitamin K is a cofactor for gamma-glutamyl carboxylase, involved in post-translational carboxylation. It is a fat soluble vitamin and requires bile salts for its absorption. Causes of vitamin K deficiency are shown in **Table 3**.

Classification

Early vitamin K deficiency bleeding disorder (VKDBD): Formerly called classic hemorrhagic disease of the newborn. It is seen usually in 1–14 days of life. Causes of this early deficiency include poor placental transfer of vitamin K, sterile gut of neonate, and inadequate oral intake in initial few days of life. It mostly occurs in breastfed infants due to low vitamin K content in breastmilk (1.5 µg/L).

Late VKDBD It is mostly seen at 2–12 weeks of age. It can also be seen up to 6 months of age. Causes of late VKDBD include low vitamin K level in breastfed infants, malabsorption, liver disease (biliary atresia, alpha-1 antitrypsin deficiency).

Third form can be seen any time after birth of later. It usually occurs secondary to maternal ingestion of drugs such as warfarin, phenytoin, phenobarbitone which following placental transfer interfere with vitamin K absorption.

Conditions associated with vitamin K dependent factor deficiency are listed in **Box 1**.

Clinical Features

Vitamin K deficiency bleeding disorder presents with bleeding most commonly from gastrointestinal tract, umbilical stump bleed, circumcision site bleed, mucosal and cutaneous bleed. Intracranial bleed is most commonly seen in late VKDBD. Vitamin K deficiency due to fat malabsorption can occur at any age. Some of the important aspects should be asked in history such as gestation at delivery, drug intake, feeding history including breastfeed and bottlefeed.

Investigations

Prothrombin time is prolonged. aPTT is usually prolonged, but it can be normal in early deficiency. In mild vitamin K deficiency, sometimes, PT may be normal. To detect mild deficiency, the undercarboxylated forms of proteins which are normally carboxylated in presence of vitamin K [proteins induced in vitamin K absence (PIVKA)] are increased.

Table 2A Interpretation of mixing studies

Defect in test plasma	Normal plasma	APTT	Aged or factor VIII deficient	Adsorbed or factor IX deficient
Factor VIII	Correction	Abnormal	No correction	Correction
Factor IX	Correction	Abnormal	Correction	No correction
Factor XI/XII	Correction	Abnormal	Correction	Correction
Inhibitor	No correction	Abnormal	No correction	No correction

Table 2B Interpretation of mixing studies

Defect in test plasma	Normal plasma	PT	APTT	Aged plasma	Adsorbed plasma
Factor II	Correction	Abnormal	Abnormal	Correction	No correction
Factor V	Correction	Abnormal	Abnormal	No correction	Correction
Factor VII	Correction	Abnormal	Normal	Correction	No correction
Factor X	Correction	Abnormal	Abnormal	Correction	No correction

Table 3 Laboratory diagnosis of coagulation disorders

<ul style="list-style-type: none"> • Normal screening test with bleeding disorder <ul style="list-style-type: none"> – Factor XIII deficiency – Mild clotting factor deficiency – Vascular disorders – Scurvy – Henoch-Schloein purpura – Senile purpura – Alpha-1 antiplasmin deficiency
<ul style="list-style-type: none"> • Isolated prolongation of prothrombin time <ul style="list-style-type: none"> – Congenital deficiency of factor VII – <i>Acquired deficiency of factor VII</i>: Drug-induced (warfarin, etc.), mild liver disease
<ul style="list-style-type: none"> • Isolated prolongation of aPTT <ul style="list-style-type: none"> – Congenital deficiency of intrinsic pathway factors [VII, IX, XI, XII, prekallikrein, high-molecular-weight kininogen (HMWK)] – <i>Presence of circulating inhibitors</i>: Diagnosis confirmed by Bethesda assay – Drugs such as heparin – <i>vWD</i>: If prolong aPTT associated with prolonged BT. The deficiency confirmed by vWF ristocetin cofactor assay – <i>Lupus anticoagulant</i>: Confirmed by kaolin clotting tests, dilute Russell viper venom test.
<ul style="list-style-type: none"> • Prolongation of both PT and aPTT <ul style="list-style-type: none"> – Deficiency of common pathway factors (factor I, II, V, X) – Combined deficiency of factors such as factor V and VIII – Acquired causes: <ul style="list-style-type: none"> - <i>Disseminated intravascular coagulation</i>: Confirmed by D dimer, fibrin degradation products - <i>Fibrinolysis</i>: Confirmed by normal D dimer and abnormal fibrin degradation products - <i>Liver disease</i>: Confirmed by SGOT/SGPT - <i>Vitamin K deficiency</i>: Confirmed by repeating PT after vitamin K injection.
<ul style="list-style-type: none"> • Prolongation of PT, aPTT, TT <ul style="list-style-type: none"> – Hypofibrinogenemias, dysfibrinogenemia – Heparin – Liver disease.

BOX 1 Conditions associated with vitamin K dependent factor deficiency

- *Dietary deficiency*: Low vitamin K levels in human milk (1.5 µg/L)
- *Malabsorption*: Celiac disease, biliary atresia, cystic fibrosis
- *Drugs*: Maternal intake of warfarin, valproate, carbamazepine, antitubercular drugs
- *Antibiotics*: Prolonged use
- *Liver diseases*: Cholestasis, acute hepatitis, Wilson disease, cirrhosis, Reye syndrome.

Treatment

When VKDBD is suspected, injection vitamin K (1 mg) is given as soon as possible. It should not be given intramuscular because of risk of hematoma formation. Babies with severe bleed (intracranial and other massive bleed) should be given fresh frozen plasma along with vitamin K to stop the bleed. Children with underlying malabsorption require high doses of oral vitamin K (2.5 mg twice a week to 5 mg/day). PT usually decreases by 6 hours. In exclusive breastfed infants, single intramuscular administration at birth is effective in preventing VKDBD.

von WILLEBRAND DISEASE

von Willebrand disease is an autosomal inherited congenital disorder. It is caused by missing or defective von Willebrand factor (vWF), a clotting protein. von Willebrand factor binds to factor VIII and platelet in blood vessels, helps in platelet plug formation during the clotting process. It is a large multimeric glycoprotein produced in megakaryocytes and endothelial cells as pre-pro form. vWF is produced by sequential cleavage. It is present in normal amount in plasma. Deficiency of vWF causes mucocutaneous bleed and bleed following trauma and surgery. It is one of the common bleeding disorders, seen in 0.1% of population (both biochemical evidence and clinical history). **Table 4** shows types of vWD.

Clinical Features

Patients usually present with nose bleed, increased bleeding during surgical procedures like dental procedures, easy bruisability, and menorrhagia.

- *Type 1 vWD* It is the most common disorder among all types (70–80%). There is qualitative deficiency of vWF, with levels of vWF in blood being 20–50% of normal. This presents with mild symptoms.
- *Type 2 vWD* It is seen in 15–30% of patients. There is qualitative defect in vWF. There are four subtypes of type 2 vWD, viz., type 2A, type 2B, type 2M and type 2N. Symptoms are usually mild to moderate in this type.
- *Type 3 vWD* These patients have qualitative deficiency of vWF. This presents with severe bleeding disorder, such as spontaneous bleeding in joints, and muscles. The level of factor 8 and vWF in plasma are almost undetectable in these patients.
- *Platelet type pseudo-vWD* It is a platelet disorder, which is phenotypically similar to type 2B vWD. There is mutation defect in *GP1BA* gene leading to abnormal *GP1b-1X* in platelet receptors. Increased binding of vWF to platelet receptors causes activation of platelet and as a result, vWF is removed from circulation. So, there are decreased levels of vWF in plasma.

Table 4 Mode of inheritance, relevant investigations to differentiate types of von Willebrand disease (vWD)

	Type 1	Type 2A	Type 2B	Type 2N	Type 2M	Type 3	Platelet type pseudo-vWD
Genetic transmission	AD	AD	AD	AR	AD	AR	AD
Frequency (%)	70–80	10–12	3–5	1–2	1–2	1–3	1–3
Factor VIII	↓	N	N	↓↓	N	Absent	N
Platelet count	N	N	N/↓	N	N	N	↓
Bleeding time	N	↓	NR/↓	N	↓	NR	NR
Response to DDAVP, factor VIII, vWF Ag test	↑	↑	↑	↑	↑	NR	↑
vWF Ag	↓	↓	N/↓	↓	N	Absent	N/↓
vWF activity	↓	↓	N/↓	↓	↓	Absent	N/↓

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; N, normal; NR, nonreactive; ↑, increased; ↓, decreased

- **Acquired vWD** It is seen in a person who does not have lifelong bleeding disorder, but presence with decreased level of von Willebrand antigen. Conditions which may be associated with acquired vWD are Wilms tumor, systemic lupus erythematosus (SLE), polycythemia vera, heart diseases, angiodysplastic lesion, lymphoproliferative disorders and drugs. The proposed mechanisms are formation of autoantibodies, adsorption onto malignant cell clones, and specific hemostatic disorders.

Management

After detailed clinical history and family history, tests are performed to evaluate the clotting time and ability of patient to form clot. Clotting factor assay and platelet function tests are done. vWF antigen test measures the amount of vWF in patient plasma. Patient with vWD will have less than 50% of normal vWF in plasma.

Mainstay of treatment of vWD disease is desmopressin acetate (DDAVP). It acts by stimulating the release of vWF from the cells which also increases factor A. It is available in two forms: injectable and nasal spray. Antifibrinolytic drugs like aminocaproic acid, tranexamic acid are used to prevent the breakdown of blood clots. These drugs are usually used before dental procedures, menorrhagia, nasal and mouth bleeds.

Type 1 vWD DDAVP is helpful in most of these patients. It normalizes factor VIII, vWF and BT. Response to DDAVP is individualized in these patients and repeat dosing may be required. Care should be taken when repeat doses are used, and it can cause tachyphylaxis.

Type 2A vWD Treatment with DDAVP increases the factor VIII levels with improvement in BT in some of the patients. Most of these patients are treated with DDAVP but some patients require treatment with clotting factor concentrates containing both vWF and factor VIII.

Type 2B vWD Clotting factor concentrates containing both factor VIII and vWF are mainstay of treatment in these patients. DDAVP is not used because it can cause transient thrombocytopenia following clearance of abnormal vWF.

Type 2N vWD DDAVP infusion is used in these patients as factor VIII levels increase after the infusion but the released factor VIII has short half-life because of impaired binding to vWF. So, for major surgery and bleeds, factor VIII concentrates with high levels of vWF are used.

Type 2M vWD The heterozygous variants of this subtype respond well to standard doses of DDAVP. But in homozygotes, the vWF released by DDAVP is defective and poor response occurs; so, vWF replacement therapy is used.

Type 3 vWD Treatment with vWF containing factor 8 concentrates is used. Since the levels of vWF in plasma are undetectable, so no releasable stores of vWF are available for DDAVP to act. Patients who have developed alloantibodies to vWF due to repeated transfusion are given recombinant factor VIII (devoid of vWF), as anaphylaxis can occur with vWF in them. The half-life of factor VIII in absence of vWF is short; so continued or repeated infusions are given.

Platelet type pseudo vWD These patients are treated by platelet transfusion.

Acquired vWD DDAVP and plasma-derived factor VIII/vWF are used in these patients. The underlying cause is treated.

Removal of antibodies is done by intravenous immunoglobulin, plasmapheresis, and immunosuppressive therapy.

FACTOR XIII (FIBRIN STABILIZING FACTOR) DEFICIENCY

It is the rarest factor deficiency. It is inherited as autosomal recessive pattern. Activated form of factor XIII leads to formation of cross-linked polymers of fibrin, which help in clot formation. It provides stability to the clot. It presents with umbilical stump bleed in up to 80% of patients, spontaneous intracranial bleed, nasal and mouth bleed, muscle bleed, hematuria, postsurgery bleed. Diagnosis is made by factor XIII assay and clot solubility test (5 M urea). Clotting tests may be normal, as patient with factor XIII deficiency forms clot.

These modalities can be used for treatment like factor XIII concentrates, fresh frozen plasma, and cryoprecipitate.

IN A NUTSHELL

1. Common coagulation abnormalities include deficiency of factor VIII and factor IX. These have been discussed earlier. Deficiencies of factors V, VII, X, and XIII are rare.
2. Mixing studies are done to identify the specific deficiency of clotting factors.
3. Among the other factor deficiencies, vitamin K deficiency is frequent, especially in infants. It can present in first 2 weeks of life (Early VKDBD—formerly called classic hemorrhagic disease of the newborn), between 2 to 12 weeks of age (late VKDBD), or later.
4. Single dose vitamin K administration at birth is effective in preventing VKDBD.
5. von Willebrand factor binds to factor VIII and platelet in blood vessels, helps in platelet plug formation during the clotting process. Patients with vWD usually present with nose bleed, increased bleeding during surgical procedures like dental procedures, easy bruisability, and menorrhagia. Mainstay of treatment of vWD disease is DDAVP.
6. Factor XIII deficiency presents with umbilical stump bleed in up to 80% of patients, spontaneous intracranial bleed, nasal and mouth bleed, muscle bleed, hematuria, and postsurgery bleed. Diagnosis is made by factor XIII assay and clot solubility test.

MORE ON THIS TOPIC

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Chapter 38.19

Thrombocytopenia

Amita Trehan

Thrombocytopenia is defined as a platelet count below $100,000/\text{mm}^3$. Its prevalence is variable in newborn, infancy and childhood. Clinical features include variable clinical symptoms depending upon the age of the child and underlying diagnosis. Detailed family history of drugs intake during pregnancy, maternal platelet count and mother's illness are helpful in establishing the diagnosis. Algorithms are helpful as an approach to a bleeding neonate or child (**Flowcharts 1 and 2**). A megakaryoblast is a product of hematopoietic stem cell differentiation. The megakaryoblast matures into the megakaryocyte, which is a large cell. This cell has a nucleus with many lobes. Platelets are fragments of cytoplasm from the megakaryocyte. Platelets have a life span of 9–10 days. Old platelets undergo phagocytosis primarily in the spleen.

A platelet count of less than $100,000/\text{mm}^3$ is termed as thrombocytopenia. Platelets are primarily responsible for maintenance of hemostasis in the body (see chapter 38.15). There are many ways to approach a child with thrombocytopenia. This may be (1) depending on the size of the platelets; (2) inherited or acquired causes; and (3) the pathogenic mechanism behind thrombocytopenia: decreased production, increased destruction and splenic sequestration (**Box 1**).

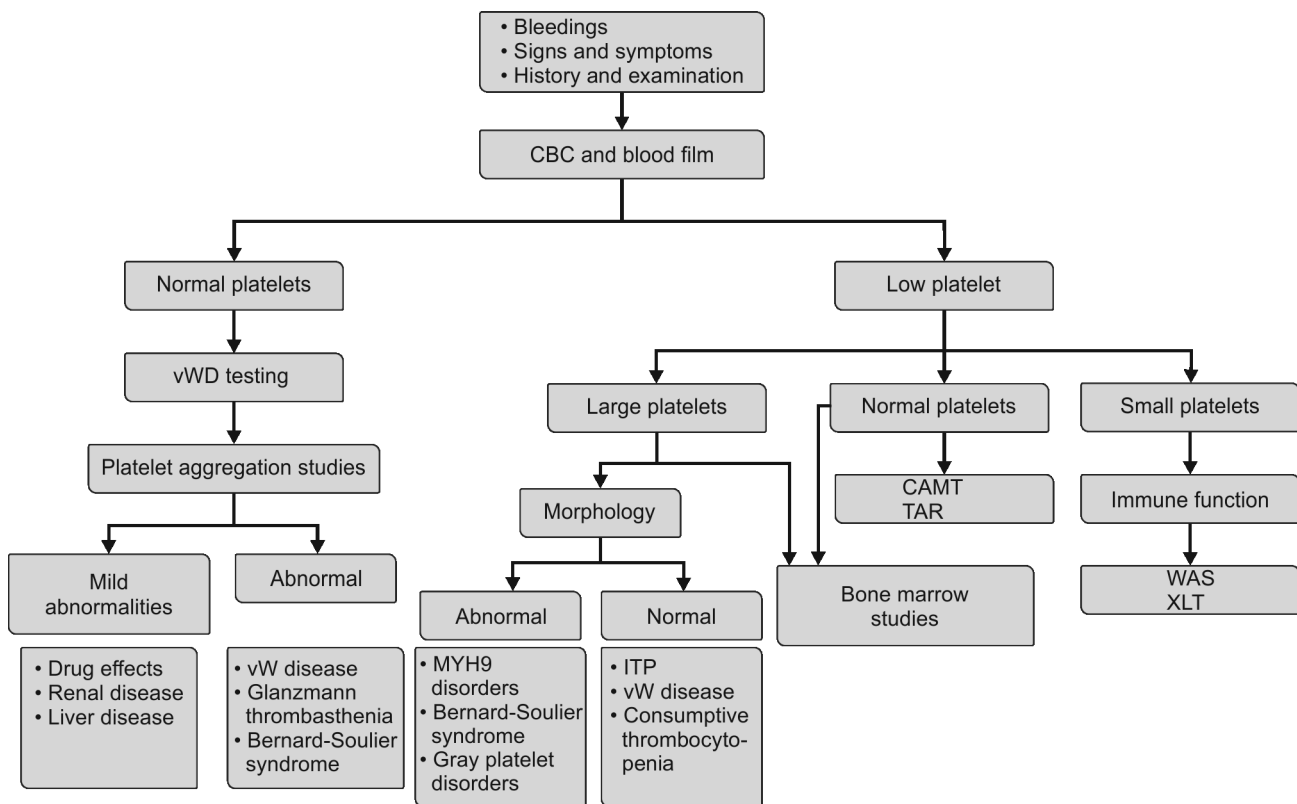
CLINICAL FEATURES

Petechiae, bruises or purpura, mucus membrane bleeding; epistaxis; gingival bleed, acute gastrointestinal bleeding, menorrhagia, hematuria, intracranial hemorrhage (ICH), etc. It is unusual for patients to bleed unless platelets fall to less than $70,000/\text{mm}^3$. Spontaneous bleeds can occur when platelets are less than $50,000/\text{mm}^3$. Major bleeding manifestations and life-threatening hemorrhages usually occur with a platelet count of less than $10,000/\text{mm}^3$.

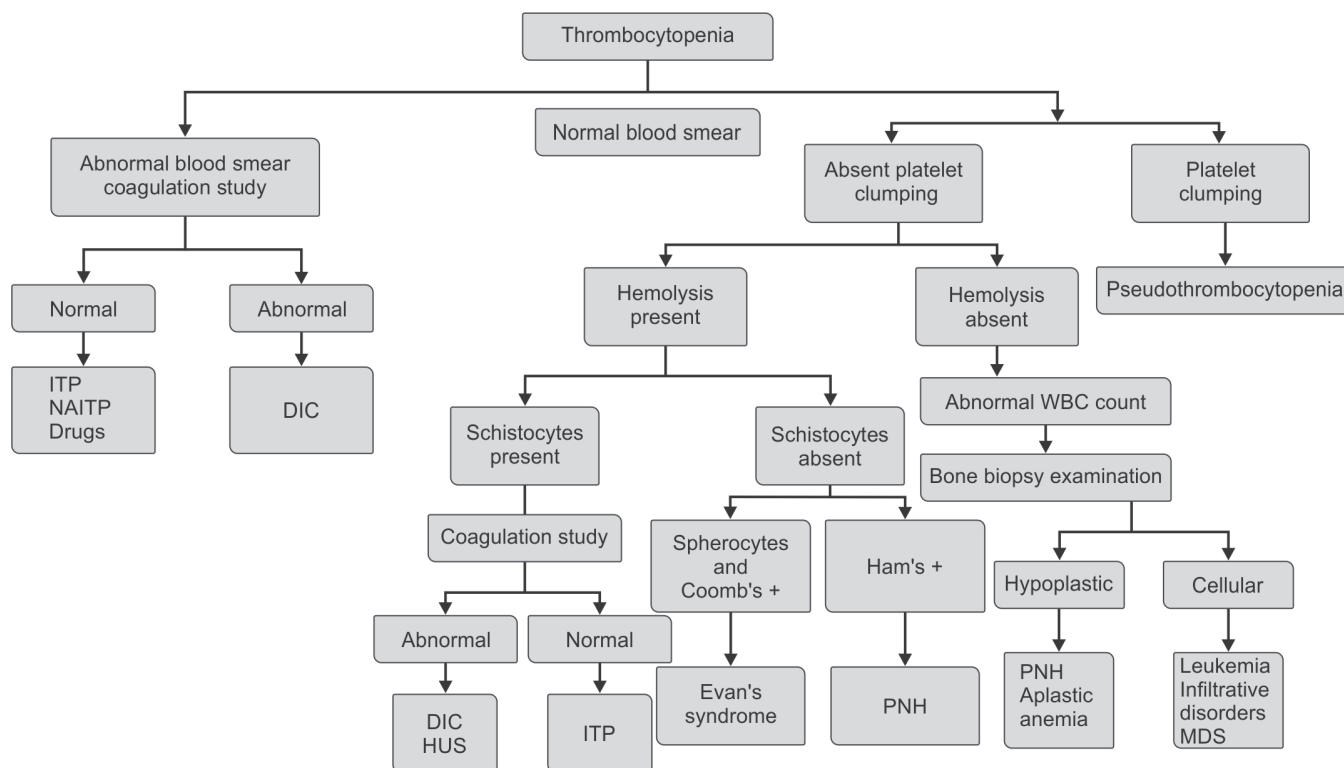
EVALUATION

A good history is mandatory and helps in establishing the etiopathogenesis of the disorder. One must look for a history of constitutional symptoms (fever, weight loss, etc.) which would be present in case of a malignancy/infection. The source of bleeding and the amount of blood lost needs evaluation. Any associated symptoms of diarrhea, respiratory infection, oliguria, vaccination, medications and family history of a similar disorder can provide vital clues to the etiology of bleed. Umbilical stump bleeding, cephalhematoma, bleeding after circumcision, conjunctival hemorrhage, hematuria are important clues in a child. The physical examination must include a thorough systemic and neurological examination. The location and severity of the bleed needs attention. Patients with thrombocytopenia typically experience mucocutaneous bleeding. Joint and soft tissue bleeding is usually seen in the presence of coagulation abnormalities.

Flow chart 1 Algorithm for approach to a bleeding child



Abbreviations: ITP, immune thrombocytopenic purpura; vW, von Willebrand; CAMT, congenital amegakaryocytic thrombocytopenia; TAR, thrombocytopenia with absent radius; WAS, Wiskott-Aldrich syndrome, XLT, X-linked thrombocytopenia; MYH9, mutations of nonmuscle heavy chain gene.

Flow chart 2 Algorithm for approach to thrombocytopenia

Abbreviations: ITP, immune thrombocytopenic purpura; DIC, disseminated intravascular coagulation; NAITP, neonatal alloimmune thrombocytopenia; PNH, paroxysmal nocturnal hemoglobinuria; HUS, hemolytic uremic syndrome; MDS, myelodysplastic syndromes

BOX 1 Causes of thrombocytopenia

Decreased platelet production

- **Viral infections:**
 - Parvovirus
 - Rubella
 - Mumps
 - Varicella
 - Hepatitis C
 - Epstein-Barr virus
 - HIV
- Aplastic anemia
- Chemotherapy
- **Cancer:** Involving and infiltrating the marrow
- Deficiency of vitamin B₁₂ and folic acid

Increased platelet destruction

- Immune-mediated
 - **Drugs:** Carbamazepine, phenytoin, valproate, phenobarb, Digoxin, Quinine, Actaminophen, Rifampin, ethambutol, piperacillin, amoxicillin, sulphamethoxazole/trimethoprim, vancomycin, ciprofloxacin, clindamycin, Heparin
 - Immune thrombocytopenia
 - Autoimmune disorders: Systemic lupus erythematosus, juvenile idiopathic arthritis
 - Transfusion of blood products and organ transplantation
- Nonimmune-mediated
 - Hemolytic uremic syndrome and thrombotic thrombocytopenia purpura
 - Disseminated intravascular coagulopathy (DIC)
 - Severe sepsis resulting in consumptive thrombocytopenia (without DIC)
- Splenic sequestration
 - Portal hypertension secondary to chronic liver disease.

INVESTIGATIONS

Blood samples should be taken before commencement of any therapy. These tests are very sensitive and a faulty sample collection will result in false results. For platelet quantitative assessment, blood anticoagulated with ethylenediaminetetraacetic acid (EDTA) is required. Tests for coagulation, the individual coagulation factors, and D-dimers are measured using blood anticoagulated with citrate. Vacutainers are preferred. The ratio of citrate to blood should be 1:9. Any faulty ratio will result in an erroneous result.

Platelet Estiation

A quantitative platelet disorder should be looked in all patients with a bleeding disorder. A platelet count is essential which may be analyzed either manually, with semiautomated counters or with a fully automated cell counter. Examination of a blood smear allows for quick estimation of platelet numbers. In automated counters, platelet clumping can result in artifactually low counts. A decreased platelet count should always be corroborated on a peripheral blood film examination. The count may also be repeated on a freshly drawn blood sample. A high platelet count may be seen in the presence of microspherocytes, leukemia cell fragments and Pappenheimer bodies. Peripheral blood film is the most important investigation which directs in the diagnostic approach in a patient with thrombocytopenia. All three blood lineages should be assessed carefully. A critically ill patient needs urgent evaluation for leukemia, disseminated intravascular coagulation (DIC), and thrombotic microangiopathy.

Bleeding Time

This is the rate at which a stable platelet plug is formed. It does not differentiate between thrombocytopenia and platelet dysfunction. In addition, as no two skin areas are the same and a standard

wound cannot be produced, the bleeding time is considered a very poor test. The American Society of Clinical Pathologists has concluded that this is not a good screening test and its usage has been abandoned.

Additional Investigations

Thrombocytopenia may be the end result of a pathogenic mechanism, therefore renal function tests, liver function tests and a coagulogram with D-dimers is required. Investigations are based upon clinical history, physical findings, clinical diagnosis and the results of the peripheral blood smear. A bone marrow aspirate may be needed to rule out a primary bone marrow disorder. In inherited disorders, mean platelet volume is helpful for further investigation. Automated counts are less accurate in the presence of micro/macro thrombocytopenia and a Wrights or May-Grunwald-Giemsa stained peripheral smear is essential regarding size, quantitative assessment, clumping and granularity.

INHERITED CAUSES OF THROMBOCYTOPENIA

In children, inherited disorders are uncommon but have to be considered as a cause of thrombocytopenia. These conditions arise as a result of a genetic defect in the megakaryocytic production. The easiest way to distinguish inherited causes is based on the size of the platelets, as small and large platelets occur in some important inherited thrombocytopenias.

Small Platelets

Wiskott-Aldrich syndrome This is a congenital X-linked disorder. It is characterized by thrombocytopenia (small platelets 3–5 fL in size), eczema and immunodeficiency. It usually presents in infancy or early childhood.

X-linked thrombocytopenia This is a less severe form of *Wiskott-Aldrich syndrome* caused by mutations in the same gene. Infectious complications and eczema are not seen in this situation.

Normal-Sized Platelets

Congenital amegakaryocytic thrombocytopenia This presents early in life as an isolated thrombocytopenia. This condition may progress to a bone marrow failure syndrome.

Thrombocytopenia absent radii (TAR) syndrome There is markedly diminished megakaryopoiesis. This manifests early in life and spontaneous recovery may occur by one year of age. TAR has a predisposition to a myeloid malignancy.

Amegakaryocytic thrombocytopenia with radioulnar synostosis This has moderate-to-severe thrombocytopenia with fusion of the radius and ulna. The thrombocytopenia persists with age.

von Willebrand disease It is an inherited disorder of von Willebrand factor (vWF). Type 2B is associated with mild thrombocytopenia. Mucocutaneous bleeding is the hallmark of this condition. Epistaxis and easy bruising is a typical history. Laboratory test for ristocetin cofactor activity and VWF multimer assay is required. Thrombocytopenia is seen in type 2B and platelet type non-Willebrand disease. In von Willebrand disease, thrombocytopenia is because of increased binding between larger non-Willebrand factor multimers and platelets. This results in the formation of platelet aggregates which get phagocytosed from the circulation resulting in a low count.

Giant Platelet Disorders

These are rare disorders in which platelets are very large (>12 fL).

Bernard-Soulier syndrome This is an autosomal recessive disorder characterized by mild thrombocytopenia, marked platelet dys-

function and bleeding symptoms which includes easy bruising and hemorrhage following an injury. The bleeding is disproportionate to the thrombocytopenia, as there is concomitant platelet function abnormality.

MYH9-related disorders Mutations of the nonmuscle heavy chain gene (*MYH9*) result in a hereditary macrothrombocytopenia with somatic abnormalities. Mild-to-moderate thrombocytopenia is observed. Nephropathy and deafness may occur and are related to the same gene mutation.

Paris-Trousseau syndrome This is a rare condition with mild-to-moderate thrombocytopenia with large platelets. It is associated with mental retardation, head and face dysmorphism, cardiac and renal defects.

X-linked thrombocytopenia with dyserythropoiesis This is due to *GATA-1* mutations on the chromosome which results in defective maturation of megakaryocytes.

NEONATAL THROMBOCYTOPENIA

Neonatal thrombocytopenia occurs in 1–3% of healthy term infants and in 20–30% of sick neonates. In a sick neonate, thrombocytopenia is usually secondary to severe illness such as sepsis, DIC, respiratory distress syndrome or due to maternal factors such as intrauterine growth retardation (IUGR), pregnancy-induced hypertension and gestational diabetes (**Box 2**).

Neonatal Alloimmune Thrombocytopenia

Neonatal alloimmune thrombocytopenia (NAIT) is a consequence of the transfer of platelet antibodies from the mother to the fetus. It is one of the commonest causes of thrombocytopenia in

BOX 2 Causes of neonatal thrombocytopenia

- Neonatal alloimmune thrombocytopenia
- Neonatal autoimmune thrombocytopenia
- Thrombocytopenia secondary to congenital infections
 - Group B *Streptococcus*
 - *Listeria monocytogenes*
 - *E. coli*
 - Toxoplasmosis
 - Rubella
 - Cytomegalovirus
 - Herpes simplex
 - HIV
- Thrombocytopenia with erythroblastosis fetalis or exchange transfusion
- Associated with maternal problems
 - Diabetes
 - Hypertension
 - IUGR
 - Perinatal asphyxia
- Late-onset thrombocytopenia
 - Sepsis
 - Necrotizing enterocolitis
 - Liver disease
- Rare causes
 - Chromosomal abnormalities
 - Inborn errors of metabolism
 - Osteopetrosis
 - Gaucher disease
 - Niemann-Pick disease
- Hemophagocytic lymphohistiocytosis
- Congenital leukemia
- Metabolic causes
 - Methylmalonic acidemia
 - Isovaleric acidemia
 - Giant hemanogios.

the newborn and is seen in 1/1,000 births. It invariably resolves within 2–4 weeks. This occurs as mothers who do not have the platelet-specific surface antigen develop alloantibodies to the paternally derived antigens when they are expressed on fetal platelets. Maternal alloantibodies attack the fetal platelets which have the platelet-specific antigens inherited from the father on their surface. Seventy five percent cases of NAIT are because of the platelet-specific antigen (P1A1), human platelet antigen (HPA-1a), followed by HPA-5b in 15–20% cases. The pathophysiology is similar to erythroblastosis fetalis. Antibodies develop by 20th week of gestation. Alloimmunization develops during the first pregnancy and recurs in more than 80% cases in subsequent pregnancies. Usually, succeeding pregnancies have more severe disease.

Clinical Features

Babies with NAIT are usually full-term babies. They are seen to develop generalized petechiae soon after birth or are born with petechiae and ecchymosis. They may have cephalhematomas, bleeding from the umbilicus and skin puncture sites in addition to visceral bleeding such as gastrointestinal or renal tract. A high incidence of ICH (up to 10–20%) is seen in babies. This is characteristically an intraparenchymal bleed. Mortality of 6–14% has been seen. These babies have a low platelet count at birth, invariably being less than 50,000/mm³.

Diagnosis

Neonatal alloimmune thrombocytopenia should be considered in all newborns with thrombocytopenia. Most cases (90%) have a platelet count of less than 50,000/mm³. A definite diagnosis needs presence of platelet antigen incompatibility in parents.

Neonatal Autoimmune Thrombocytopenia

Mothers with isolated immune thrombocytopenia (ITP) have autoantibodies. These antibodies can cross over passively through the placenta to the fetus. The same phenomenon occurs as in autoimmune disorders like systemic lupus erythematosus (SLE). These babies are well at birth. A maternal platelet count helps in clinching the diagnosis and distinguishes this from NAIT. In addition, the history and platelet count should be available before/during pregnancy. This condition is less severe than NAIT, with only 10–15% babies having a platelet count of less than 50,000/mm³. The bleeding manifestations are fewer and the risk of ICH rare. In this condition, maternal antibodies are transferred passively across the placenta and attack the fetal antigens. The antigens commonly involved are the glycoprotein (GPIIb/IIIa or GB1b/IX) complexes. Babies with significant bleeds require therapy. In addition, therapy is recommended in asymptomatic babies with a count below 30,000/mm³.

Management

Platelet transfusion at 10–20 mL/kg is given. Random donor platelets are sufficient. Matched platelets have not been seen to offer any added advantage. Intravenous immunoglobulin 1 g/kg/day for 1–3 days may be given. Methylprednisolone (1 mg IV) 8 hourly is administered along with IVIG. Follow-up till normal platelet counts are achieved is mandatory.

Thrombocytopenia Associated with Erythroblastosis Fetalis or Exchange Transfusion

Babies with erythroblastosis may have skin bleeds soon after birth. The pathophysiology is related to an immune mechanism. It may also be secondary to a very high bilirubin level which can affect the platelet survival. Often, there may be thrombocytopenia following an exchange transfusion secondary to decreased platelets in the blood used.

Thrombocytopenia Secondary to Intrauterine Growth Retardation, Hypoxia, Maternal Diabetes and Pregnancy-induced Hypertension

Any condition which has placental insufficiency can result in thrombocytopenia. This will include pregnancy-induced maternal diabetes mellitus, hypertension, IUGR and perinatal asphyxia. The pathophysiology is impaired megakaryopoiesis which also results in an elevated thrombopoietin level. Increased platelet destruction has also been seen in these conditions. Thrombocytopenia is invariably self-limited needing no therapy. The nadir is likely to occur around day four with recovery by the end of the first 2 weeks of life.

Thrombocytopenia Secondary to Congenital Infections

A perinatal infection is the commonest cause of severe thrombocytopenia that occurs within 72 hours, especially in a sick neonate. Infections needing exclusion include: group B *Streptococcus*; *Listeria monocytogenes*; *Escherichia coli*; toxoplasmosis, rubella, cytomegalovirus, herpes simplex (TORCH) infections and HIV. Amongst the TORCH infections, cytomegalovirus (CMV) infection is the commonest to be associated with severe thrombocytopenia. Jaundice, pallor and hepatosplenomegaly may be present and are considered to be a hallmark in infants with congenital infections. The described *blueberry muffin* rash is secondary to extramedullary hematopoiesis.

Thrombocytopenia is seen secondary to sepsis because of:

- Disseminated intravascular coagulation resulting in consumptive thrombocytopenia
- The phagocytic system clears the bacteria, viruses and immune complexes in any infection. Platelets stick to all three and as a result get phagocytized also.
- There is suppression of the bone marrow secondary to sepsis. This contributes to thrombocytopenia which reverts when the infection is controlled.

Late-onset thrombocytopenia secondary to late-onset or hospital-acquired infections Thrombocytopenia seen after the first week of life is usually secondary to sepsis. Decreased immunoglobulin level as a result of prematurity per se contributes to these processes.

Thrombocytopenia due to Aneuploidy

Nearly 85% cases of Down's syndrome may have thrombocytopenia. This may be due to transient myeloproliferative syndrome which is seen in Down's syndrome. Thrombocytopenia may also occur in trisomy 13, trisomy 18, Turner's syndrome and triploidy. Associated congenital anomalies in these cases are a clue to the diagnosis.

Inborn Errors of Metabolism/Rare Disorders

These include osteopetrosis, metastatic neuroblastoma, Gaucher disease, Niemann-Pick disease, hemophagocytic lymphohistiocytosis, afibrinogenemia and congenital leukemia.

Metabolic Causes

Hyperglycinemia with ketosis and methylmalonic acidemia present with lethargy, vomiting and ketosis during the neonatal period. These disorders may cause episodic thrombocytopenia and neutropenia during infancy. Isovaleric acidemia is associated with generalized marrow hypoplasia resulting in thrombocytopenia and neutropenia.

Platelet Destruction

Immune-mediated Platelet Destruction

Drug-induced thrombocytopenia This is a result of a drug-dependent antibody which forms against an antigen on the surface of the platelet. Thrombocytopenia in this situation is moderate to

severe with clinical manifestations corresponding to the platelet count. It invariably develops a few days to 1–3 weeks of starting the drug. This condition can be easily confused with ITP, thereby highlighting the importance of a drug history. It usually resolves within a week to ten days of stopping the drug. The diagnosis is essentially clinical, a laboratory diagnosis being possible only by demonstration of the drug-dependent antibody. Common drugs which result in thrombocytopenia are given in **Box 1**.

Heparin-induced thrombocytopenia A small percentage (0.5–5%) of heparin-treated subjects develop heparin-induced thrombocytopenia (HIT). A fall in platelet count by $\geq 50\%$ from the baseline should alert one to the diagnosis of HIT. The thrombocytopenia is usually moderate with a varied clinical picture which includes venous and arterial thrombosis and necrotic skin lesions. This condition usually develops 5–10 days after initiation of heparin therapy. HIT is a consequence to development of antibodies against the heparin PF-4 complex, and C-serotonin release assay is diagnostic of the same. In such a situation, it is advisable to use other anticoagulants if required.

Immune thrombocytopenia The commonest acquired bleeding disorder in childhood universally is ITP. It is generally self-limiting but may have a chronic or recurrent course. Eighty to ninety percent children have an acute transient episode of thrombocytopenia which resolves in a few weeks. Children with immune thrombocytopenia usually present between 2 and 10 years of age. They generally present with an acute history of presence of petechiae/purpuric spots in an otherwise fit child. A history of a recent viral illness is often forthcoming. The clinical manifestations, diagnosis, and management of ITP in children are discussed in a separate chapter.

Systemic lupus erythematosus Thrombocytopenia may be the presenting feature in SLE. The other symptoms may appear much later. Three to fifteen percent of patients with thrombocytopenia may develop SLE. Mild thrombocytopenia is seen in patients with SLE. A very small percentage of patients have a moderately low platelet count of less than $50,000/\text{mm}^3$. The pathophysiology of thrombocytopenia in SLE is generally immune-mediated platelet destruction. In SLE, platelet consumption may also occur as a result of microangiopathic hemolytic anemia with ensuing thrombocytopenia.

Nonimmune-mediated Platelet Destruction

Certain conditions like hemolytic uremic syndrome (HUS), thrombotic thrombocytopenic purpura (TTP) and DIC have thrombocytopenia as a result of platelet activation, aggregation and consumption. Kasabach-Merritt syndrome results in thrombocytopenia as a result of coagulation and platelet trapping in the hemangioma.

Disseminated intravascular coagulation It is a condition where there is activation of intravascular coagulation. This results in the formation of microvascular thrombi. In addition, there is thrombocytopenia and reduction of clotting factors. The acute form of DIC can also be seen in severe sepsis, septic shock, neurotrauma, ABO incompatible blood transfusion and in acute promyelocytic leukemia. Thrombocytopenia is moderate to severe and the bleeding manifestations are usually severe.

Chronic disseminated intravascular coagulation It is usually seen with solid tumors, large aortic aneurysms and cyanotic heart disease. The thrombocytopenia in chronic DIC is mild to moderate and the bleeding manifestations milder than in an acute DIC.

Thrombotic thrombocytopenic purpura This is a syndrome characterized by hemolytic anemia, thrombocytopenia, renal dysfunction, fever and neurological symptoms. In TTP, there

is thrombotic occlusion of the microcirculation. This is a result of deficient activity of vWF factor clearing protease caused by mutations of a *disintegrin-like and metalloprotease with thrombospondin motifs* (ADAMTS 13) gene. Severe bleeding from thrombocytopenia is unusual, though skin bleeds are common. The thrombocytopenia ranges from a mild to severe state and it has been covered in detail in other section.

Hemolytic uremic syndrome Microangiopathic hemolytic anemia, thrombocytopenia and acute kidney injury constitute HUS. The thrombocytopenia is usually moderate and active bleeding is infrequent. Platelet transfusions are usually required only when an invasive procedure is required.

Giant hemangioma Thrombocytopenia as a result of consumption and platelet trapping has been seen in giant hemangiomas. This is a form of localized intravascular coagulation. Any giant hemangioma associated with consumptive thrombocytopenia is referred to as the Kasabach-Merritt syndrome. Usually, hemangiomas are cutaneous in nature. However, any child with cutaneous hemangioma needs evaluation for any deep seated visceral hemangioma, e.g., liver, spleen. In addition, infants with baffling thrombocytopenia need evaluation for visceral hemangiomas.

Mechanical destruction Extracorporeal therapies, viz., extracorporeal membrane oxygenation, cardiopulmonary bypass hemodialysis and apheresis can result in thrombocytopenia secondary to mechanical destruction.

Sequestration/trapping The spleen sequesters one-third of platelet mass. This increases in conditions associated with hypersplenism, resulting in thrombocytopenia. Leukopenia and anemia may also accompany a low platelet count.

Decreased Production of Platelets

Nutritional Deficiency

This is especially important in a country like India where there is a high incidence of folate and vitamin B₁₂ deficiency which results in impaired bone marrow production and often results in pancytopenia.

Bone Marrow Failure

A bone marrow dysfunction may be as a consequence of a malignancy of the bone marrow, e.g., leukemia. Dysfunction of the marrow also results when the marrow is invaded by a solid tumor, e.g., neuroblastoma. There may be shut down of the marrow as is seen in aplastic anemia which results in pancytopenia and thrombocytopenia. Cytotoxic drugs and radiotherapy also result in bone marrow suppression with ensuing pancytopenia. In addition, the hereditary disorders of thrombocytopenia are secondary to decreased production (described earlier).

Cyanotic Heart Disease

It has decreased production of megakaryocytes, the exact mechanism not being clear.

Infections

The common infections which may result in thrombocytopenia include Epstein-Barr virus, CMV, parvovirus, varicella, HCV and rickettsia. This thrombocytopenia is transient and recovery is usually seen within a period of a few weeks. HIV-associated thrombocytopenia was a frequent finding in patients with retroviral infection in the era prior to the development of antiretroviral therapy and 40% were seen to have thrombocytopenia during the course of their illness. This correlated with the degree of immunosuppression. Thrombocytopenia is also encountered as an initial manifestation of HIV infection in 10% patients. HIV must be ruled out in the evaluation of a child with thrombocytopenia. Immune dysregulation akin to immune thrombocytopenia is considered

as the pathogenesis for thrombocytopenia in HIV patients and is termed primary HIV-associated thrombocytopenia. In addition, there is reduced platelet count secondary to medications, infection, or thrombotic microangiopathy. Hypersplenism secondary to coincident liver disease and/or cirrhosis is another common cause of thrombocytopenia in patients with HIV infection.

IN A NUTSHELL

1. Thrombocytopenia is defined as a platelet count of less than 100,000/mm³.
2. Spontaneous bleeding is unlikely till the platelet count falls below 20,000/mm³.
3. Intracranial hemorrhage is a dreaded but rare complication.
4. Thrombocytopenia is caused by increased destruction, decreased production (congenital, infectious, marrow dysfunction) or sequestration of platelets.
5. Evaluation has to be done by an initial complete blood count with examination of the peripheral blood smear.
6. Further investigations are done depending upon the clinical evaluation of the patient.
7. Immune thrombocytopenia is the most common diagnosis of isolated thrombocytopenia in preschoolers and school-going children.
8. There is no absolute threshold for treatment, which should be decided based on clinical evaluation and an estimate of risk of significant hemorrhage.
9. Platelet transfusions have limited utility in immune-mediated disorders.

MORE ON THIS TOPIC

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Chapter 38.20

Immune Thrombocytopenic Purpura

Jagdish Chandra, Dinesh Yadav

Immune thrombocytopenic purpura is an acquired immune-mediated disorder characterized by isolated thrombocytopenia. The abbreviation, ITP, has been variably used to define *idiopathic thrombocytopenic purpura* or *immune thrombocytopenic purpura*. ITP is an autoimmune disorder characterized by destruction of otherwise normal platelets, most commonly occurring in response to an unknown stimulus. ITP may occur in isolation (primary) or in association with other disorders (secondary).

Recently, an International Working Group (IWG) has reviewed the recommendation on nomenclature and treatment which is widely being followed. This group defined thrombocytopenia as platelet count less than $100 \times 10^9/L$ based on three considerations: (1) a study demonstrating that only 6.9% patients presenting with a platelet count between 100 and $150 \times 10^9/L$ developed a persistent platelet count less than $100 \times 10^9/L$ over 10 years of follow-up; (2) recognition that in non-Western ethnicities normal values in healthy individuals may be between 100 and $150 \times 10^9/L$; and (3) the hypothesis that a cutoff value of $100 \times 10^9/L$ would reduce concern over the mild *physiologic* thrombocytopenia associated with pregnancy. This group suggested the term *immune thrombocytopenia* as many patients with ITP do not have purpura. The 'P' in ITP, has been retained to avoid altering the traditional acronym.

In place of traditional classification (acute and chronic), ITP has been reclassified as newly diagnosed, persistent and chronic ITP based on duration. These and other terminologies are defined in **Table 1**. The distinction of primary from secondary ITP is important as therapy in secondary ITP is targeted at treatment of underlying disorder. Various causes of secondary ITP are enumerated in **Table 2**.

EPIDEMIOLOGY

Childhood primary ITP has an incidence of approximately 4.0 per 100,000 children per year and usually has a self-limiting course. In a large series [Intercontinental Cooperative ITP Study Group (ICIS)] of over 2,000 cases, mean age of presentation

reported was 5.7 years. In this series, 70% were children between 1 year and 10 years, 20% from 10 to 16 years and 10% were infants (3–12 months). In young age, children of both genders are equally affected. However, slight female predominance is reported in older children (>10 years of age). Nearly 50–65% cases have a preceding viral infection, usually an upper airway infection. In addition, cases occurring after known infections such as rubella, varicella, mumps, rubeola, infectious mononucleosis and cytomegalovirus have been described. In a minority, ITP may also occur after vaccination with a live attenuated vaccine. Yet the only vaccine for which there is a demonstrable cause-effect relationship is the measles, mumps, and rubella (MMR) vaccine with one to three children every 100,000 vaccine doses developing ITP. Most children with ITP have remission with or without treatment. Only 10–20% of children have persistent thrombocytopenia 1 year after the initial diagnosis.

PATHOPHYSIOLOGY

Immune thrombocytopenic purpura is characterized by immune-mediated destruction of platelets. These antiplatelet antibodies were identified as IgG directed against glycoprotein IIb/IIIa and Ib/IX in particular. Antibodies that react with glycoprotein Ia/IIa, IV and V and other platelet determinants have also been identified and the presence of antibodies against multiple antigens is typical in ITP, presumably because of epitope spread. Once produced, these autoantibodies bind to platelets, causing their destruction by either phagocytosis or possibly complement activation and lyses. However, these autoantibodies are documented in only 75% of ITP patients. Other pathophysiological mechanisms, such as T-cell-mediated cytotoxicity, may thus be involved in platelet destruction.

Production of antiplatelet antibodies by B cells is facilitated by CD4+ T cells. Proliferation of CD4+ T cells is controlled by activated antigen presenting cells. Of the two helper T-cell cytokine profiles, ITP shows a Th1 cytokine response [elevated interleukin 2 (IL-2) and interferon- γ (IFN- γ), and reduced IL-10 levels] and a reduced Th2 response, a pattern similar to autoimmune disorders. Ongoing antibody production is necessary for chronicity of the disease.

For more than 50 years, loss of self-tolerance leading to production of autoantibodies against platelet antigens has been recognized as the underlying problem of ITP, and it was assumed that thrombopoiesis was maximized in response to the increased platelet clearance. However, evidence has emerged recently that thrombopoiesis is impaired in at least some patients. Kinetic analyses using autologous platelets demonstrated that 73% of ITP patients had normal or decreased platelet production. Platelet-associated antibody levels correlated inversely with

Table 1 ITP nomenclature (suggested by International Working Group 2009)

Newly diagnosed ITP	All new cases at diagnosis are labeled by this term up to 3-month duration.
Persistent ITP	Refers to thrombocytopenia persisting for 3–12 months from diagnosis. This category includes patients not achieving spontaneous remission or not maintaining their response after stopping therapy between 3 months and 12 months from diagnosis.
Chronic ITP	Refers to thrombocytopenia lasting for more than 12 months.
Recurrent ITP	Defined as return of thrombocytopenia/symptoms after at least 3 month of remission, sustained without treatment.
Primary ITP	Defined as isolated thrombocytopenia (immune-mediated) in the absence of underlying disorders that may be associated with thrombocytopenia. It is a diagnosis of exclusion.
Secondary ITP	Includes patients, where a specific etiology for thrombocytopenia is identified [e.g., systemic lupus erythematosus, HIV, drugs].
Severe ITP	Patients who have <i>clinically relevant bleeding</i> , i.e., bleeding symptoms that warrant treatment. It does not necessarily imply a very low platelet count.
Refractory ITP	Patient with ITP who has failed first-line therapy as well as splenectomy, and continues to experience clinically significant bleeding. More useful in adults with ITP.

Table 2 Causes of secondary immune thrombocytopenic purpura

Antiphospholipid syndrome
Systemic lupus erythematosus
Autoimmune thrombocytopenia (e.g., Evan's syndrome)
Common variable immunodeficiency
Drug administration side effect
Infection with cytomegalovirus, HIV, <i>H. pylori</i> , hepatitis C, varicella zoster
Lymphoproliferative disorders
Bone marrow transplantation side effect
Chemotherapy-induced

platelet production, suggesting that platelet antibodies impair platelet production as well. Platelet antibodies are known to bind to megakaryocyte membranes of ITP patients, and such antibodies may interfere with megakaryocyte maturation, platelet production and release. Morphologic features consistent with apoptosis have been reported to be more common in megakaryocytes of ITP patients than healthy controls. However, impaired megakaryocytopoiesis is inconsistent. Thus, ITP likely presents a mixed picture of impaired platelet production and accelerated platelet destruction. In addition, thrombopoietin (TPO) levels are normal or only slightly increased. Hence, the rate of thrombopoiesis is inadequate to counterbalance the increased rate of platelet destruction.

CLINICAL FEATURES

Immune thrombocytopenic purpura commonly presents as a sudden onset bleeding in an otherwise well child. It typically affects children in the age group of 2–6 years. Most children present with skin bleed (97%) and few have epistaxis (12–30%). Very few children (3–5%) develop severe bleeding, defined as episodes requiring hospitalization and/or blood transfusions. Intracranial hemorrhage (ICH) is a rare (incidence ~ 0.2%), though a real and potentially life-threatening complication. Circulating platelets in ITP patients, although few in number, tend to be particularly effective at hemostasis, perhaps because most will have been recently released from the marrow and are fresh, large, and granular. As a result, ITP patients are far less likely to have serious bleeding than patients with similarly low platelet counts caused by other processes such as marrow failure. Even in cases with ITP having severe thrombocytopenia, arbitrarily defined as platelet count $<20,000/\text{mm}^3$, bleeding other than skin bleeds have occurred only in 12–20% cases. Majority of children who present with or develop ICH have severe thrombocytopenia, bleeding manifestations beyond petechiae and ecchymosis (particularly hematuria) and a high rate of reported head trauma. Spleen is palpable in 5–10% of children. Malaise, bone pains and lymphadenopathy should raise concern for another cause such as acute leukemia.

Childhood ITP is a benign, self-limiting disease. The ICIS group concluded that remission occurred in 37% of the patients between 28 days and 6 months after the initial diagnosis, in 16% between 6 and 12 months and in 24% between 12 and 24 months. Several studies have identified one or more of the following factors to be associated with a shorter duration of thrombocytopenia: younger age at diagnosis (<10 -year-old), abrupt onset (<2 weeks) of symptoms, preceding viral infection, extremely low platelet count ($<5 \times 10^9/\text{L}$) and the presence of wet purpura. Also, male gender and elevated serum IgG levels at diagnosis have been associated with a good prognosis. Data from natural history suggests that adolescents are more likely to develop persistent or chronic ITP.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Diagnosis of ITP is made on clinical features, supported with laboratory parameters. Typically, the clinical features include:

- Abrupt onset of skin bleeds in a previously well child.
- *Pallor proportionate to bleeds*: Observed in 15% of children, particularly in those with epistaxis, hematuria or gastrointestinal (GI) bleed. In India, coexisting nutritional anemia is not uncommon.
- Absence of fever, lymphadenopathy, hepatosplenomegaly or bone pains.

Immune thrombocytopenic purpura is a diagnosis of exclusion. Leukemia and aplastic anemia are close differentials, which should be excluded by detailed history, physical examination and relevant laboratory investigations. Inherited thrombocytopenia should be reliably excluded in children younger than 12 months. Other differential diagnoses of thrombocytopenia in children are described in **Table 3**.

INVESTIGATIONS

There are no diagnostic tests to confirm ITP. A review of hemogram and peripheral smear by pathologist is essential. Pseudothrombocytopenia caused by platelet agglutination due to ethylenediaminetetraacetic acid (EDTA) should be reliably excluded. Typical findings include isolated (often severe) thrombocytopenia, with a normal leukocyte and differential count. Peripheral smear shows few large platelets. A low Hb with reduced mean corpuscular volume may indicate concomitant iron deficiency anemia. Macrocytosis points toward megaloblastic or aplastic anemia. Acute bleeding may result in moderate neutrophilia with occasional immature forms. Mild eosinophilia can be observed. A distinctive lymphocytosis is alarming, though it may be secondary to a resolving viral infection. Tests for HIV

Table 3 Differential diagnosis of thrombocytopenia in children

Pseudothrombocytopenia	EDTA-induced platelet clumping
Gestational/neonatal causes	Maternal pre-eclampsia, HELLP* Neonatal alloimmune thrombocytopenia Maternal drug ingestion
Inherited disorders	Thrombocytopenia absent radius syndrome Amegakaryocytosis Wiskott-Aldrich syndrome
Infectious causes	Sepsis, congenital TORCH infection Viral infections, rickettsial disease, <i>H. pylori</i> , HIV, HCV
Impaired thrombopoiesis	Aplastic anemia, Fanconi anemia Paroxysmal nocturnal hematuria, myelofibrosis Myelodysplastic syndrome, osteopetrosis
Giant platelet disorders	May-Hegglin anomaly Bernard-Soulier syndrome
Malignancy	Leukemia, lymphoproliferative disorders
Platelet sequestration/consumptive coagulopathy	Hypersplenism, Kassabach-Merritt syndrome, DIC, TTP, HUS, type 2B von Willebrand disease, purpura fulminans
Collagen vascular disorders	Systemic lupus erythematosus, antiphospholipid syndrome

*HELLP: Hemolysis, Elevated Liver enzymes, Low Platelet count

Abbreviations: EDTA, ethylenediaminetetraacetic acid; TORCH, Toxoplasma gondii, rubella virus, cytomegalovirus, and herpes simplex virus; DIC, disseminated intravascular coagulation; TTP, thrombotic thrombocytopenic purpura; HUS, hemolytic uremic syndrome

and HCV are also recommended. Exclusion of *Helicobacter pylori* is advisable in adults, if there is clinical suspicion or high local prevalence. Detection of antiplatelet, antithyroid and antinuclear antibodies is neither sensitive nor specific and has no role in the diagnosis of ITP.

The purpose of a bone marrow (BM) examination is not to diagnose ITP, but to exclude an ominous etiology of thrombocytopenia, particularly leukemia and aplastic anemia. It is unusual to overlook these disorders, if the peripheral smear has been reviewed by an experienced pathologist and not found to be atypical. It has been customary to perform a BM prior to administering steroids, for fear of masking an underlying leukemia. However, recent guidelines advocate against this practice in a typical case of acute ITP. A BM can particularly be avoided if decision has been taken for conservative management or for administering intravenous immunoglobulin (IVIG) or anti-D. A BM examination will definitely be required in presence of fever, lymphadenopathy, hepatosplenomegaly, bone/joint pains; pallor disproportionate to bleeds, and/or high or low leukocyte count, atypical cells in blood smear or macrocytosis. The recommendations on BM examination should be viewed with caution in India and other developing countries where concomitant nutritional anemia may complicate the clinical picture. Moreover, most cases will be managed by pediatricians who may be treating ITP only infrequently. In chronic ITP patients, BM evaluation should be considered, if not already done. Screening tests for immunodeficiency, systemic lupus erythematosus (SLE) and other autoimmune diseases [antinuclear antibody (ANA), direct Coombs test, antiphospholipid antibody, thyroid function tests] and serologic testing for HIV and HCV should also be considered. Obtaining blood counts and peripheral smears from the parents may help to exclude the familial disorders. Routine testing for *H. pylori* and TORCH group of infections is not recommended.

MANAGEMENT

In the modern day management of ITP, the dilemma is to balance attempts at preventing severe bleeds versus avoiding therapy-related toxicities and reducing cost of therapy. It is important to remember that: (1) majority of patients will not have life-threatening bleed; (2) disease has a self-limiting nature; (3) therapy does not modify the course of the disease; and (4) platelet count alone has never been shown to predict the severity of bleeding and (5) there is no evidence that medical therapy reduces the incidence of ICH. The principle is to treat clinically relevant bleeding episodes and not to treat the low platelet count. Hospitalization is appropriate for treatment of a child with severe bleeding episode, but otherwise not required in an uncomplicated case. The principles of treatment are shown in **Box 1**.

Observation Alone Approach

In 1966, Zuelzer and Lusher described 152 children with ITP seen between 1956 and 1964, and advised that the child, not the platelet count, should be treated. This discussion whether to treat ITP patients based on platelet count or bleeding symptoms alone, continues even after 60 years of this initial description of ITP. Earlier (1996) American Society of Hematology (ASH) guidelines recommended treatment of ITP patients based on platelet counts. However, the United Kingdom has adopted a minimalistic treatment approach to children with little or no bleeding at diagnosis of ITP since the early 1990s, with only 16% of children now receiving drug therapy compared with 61% in 1995. The ICIS group also reported the emerging trend toward reserving drug therapy for patients with major bleeds or troublesome impairment of quality of life. The United States has not experienced this same trend, but recent ASH guidelines (2011) suggest ITP treatment based on the severity of

bleeding, reliability of family for close follow-up, and potential loss of quality of life and advised *observation alone* for children with no or mild bleeding, irrespective of the platelet count.

An internationally accepted classification of various bleeding manifestations is presented in **Table 4**. Observation alone is recommended in grade 1 and most of the grade 2 bleeds, while platelet raising therapy needs to be initiated in grade 3 and grade 4 bleeds. However, fear of ICH among parents as well as treating physicians is a major hindrance in employment of these recommendations. Although there have been no randomized trials using prevention of ICH or other significant bleeding events as a clinical end point, data extrapolated from natural history studies indicate that the vast majority of children do not experience significant bleeding at follow-up. A registry of 2,540 children followed for 6 months reported three episodes (0.17%) of ICH. All 3 patients had a platelet count less than $20 \times 10^9/L$ at diagnosis and 2 of the 3 had received treatment at diagnosis. A more recent study followed 1,682 children for a minimum of 6 months and determined that only 3 (0.2%) developed ICH. There is no evidence that medical therapy, such as administration of glucocorticoids or IVIG reduces the incidence of ICH and it may occur despite prior or concomitant therapy.

The decision to manage with *observation alone* requires a detailed discussion with the family about health-related quality of life, medication side effects and efficacy, and anticipatory guidance about preventing and monitoring for bleeding. Treatment may be appropriate in children if follow-up cannot be assured or child stays at a remote place. Children with high activity level and upcoming invasive procedure with risk of bleeding should also be considered for treatment. Though evidence suggests that adolescents are more likely than younger children to develop persistent or chronic disease, there have been no studies investigating a benefit to altered treatment in this age group or the age at which this effect is likely to be most present. Therefore, the management of adolescents should follow the usual management of children with ITP.

BOX 1 Treatment principles

- Treat the patient and not the platelet count
- Grading for severity of bleeding should be employed to decide management of a particular patient
- The first-line platelet raising drugs include corticosteroids, IVIG and IV anti-D
- Second-line drugs include high-dose dexamethasone or methylprednisolone; IVIG or IV anti-D, rituximab and immunosuppressive agents
- Splenectomy should only be considered in patient with chronic ITP with significant bleeds, who fail to respond to usual first- and second-line drugs
- Emergency measures in life-threatening bleeds includes use of more than one drug (methyl prednisolone with IVIG or IV anti-D), along with frequent platelet transfusions
- Thrombopoietin agonists (eltrombopag and romiplostim) have shown encouraging results in adults, but their long-term safety and efficacy is yet to be established in children

Table 4 Grade of severity in immune thrombocytopenic purpura patients

Grade	Bleeding/quality of life
Grade 1	Minor bleeding, few petechiae (≤ 100 total) and/or ≤ 5 small bruises (≤ 3 cm diameter); no mucosal bleeding
Grade 2	Mild bleeding, many petechiae (> 100 total) and/or > 5 large bruises (> 3 cm diameter); no mucosal bleeding
Grade 3	Moderate bleeding, overt mucosal bleeding, troublesome lifestyle
Grade 4	Mucosal bleeding or suspected internal hemorrhage

First-line Therapies for Newly Diagnosed Immune Thrombocytopenic Purpura

The three first-line drugs include corticosteroids, IVIG and anti-D. The goal of all platelet raising strategies for patients with ITP is to achieve a platelet count that is associated with adequate hemostasis, rather than a *normal* platelet count.

Corticosteroids

They act through several mechanisms: (1) inhibition of phagocytosis and antibody synthesis; (2) improved platelet production, and (3) increased microvascular endothelial stability. The latter effect aids in controlling bleeding even prior to an increase in platelet count. In randomized trials, prednisolone therapy has been shown to induce more prompt normalization of platelet count than placebo does. The most traditional regimen for treating children with ITP is oral prednisolone at a dose of 2 mg/kg/day (60 mg/m²/day) for 3–4 weeks. Higher doses of parenteral steroids have also been tried and result in a rapid increase of platelet counts. Various regimens of oral and parenteral steroids, response rate and adverse effects are mentioned in **Table 5**. If corticosteroids are chosen as treatment, there is no evidence to support any dosing regimen over the other. Yet, long-term corticosteroids should be avoided in children because of the side effects.

Intravenous Immunoglobulin G

Intravenous immunoglobulin blocks Fc-receptors on the macrophages of the reticuloendothelial system and thereby slows the clearance of antibody-coated platelets. Effects on cytokines might also be important for their therapeutic effect and IVIG may also influence the number and function of regulatory T-cells. IVIG produces more rapid increase in the platelet count than traditional doses of oral prednisolone (2 mg/kg/day), as documented in controlled trials and meta-analysis. The long course of IVIG (0.4 g/kg/day for 5 days) has now been superseded by shorter course (1 g/kg/day for 2 days or a single dose of 0.8 g/kg). Recent ASH guidelines recommend single dose of IVIG (0.8–1 g/kg), if a rapid increase in platelets is desired. Both splenectomized and nonsplenectomized patients may respond to IVIG and these responses are generally reproducible. However, platelet counts fall below acceptable level after 2–6 weeks in one-third of the patients.

Cost is a major limiting factor for the use of IVIG, as it is considerably more expansive compared to steroids or anti-D. Frequent side effects of IVIG therapy include flu-like symptoms, which may be alleviated by pretreatment with antihistaminics and analgesics. Approximately 10% patients may experience aseptic meningitis, which may result in additional diagnostic studies (CT scan) and prolonged hospital stay. Anaphylaxis is another serious, but rare side effect of IVIG therapy and seen more commonly in IgA deficient patients.

IV Anti-D

It has emerged as an additional treatment for ITP over last 30 years in Rh (D) positive individuals. These anti-D antibodies coat red blood cells and engage macrophage Fc-receptors. Thus, preferential red cell destruction takes place in the reticuloendothelial system sparing the platelets. The prerequisites for anti-D treatment in ITP are that the patient should be Rh (D) positive with a hemoglobin level greater than 10 g/dL. Patient should not have undergone splenectomy and coexisting hemolytic anemia should be ruled out.

The use of anti-D in the first-line treatment of newly diagnosed ITP in children remains controversial. Randomized studies in children with ITP have reported comparable or lower efficacy of various dosing regimens of anti-D to IVIG. Similarly, studies comparing an anti-D dose of 50 µg/kg and 75 µg/kg also report contradictory results. ASH 2011 guidelines suggest use of single dose IV anti-D in Rh-positive, nonsplenectomized patients, with negative direct antiglobulin test (DAT); however, there is inconclusive evidence to recommend a specific dose. The therapeutic effect of anti-D lasts for 1–5 weeks. Less cost, shorter administration time and shorter duration of hospitalization makes the medication more convenient to use compared to IVIG.

Adverse events like headache, nausea, chills, dizziness and fever have been reported in 3% of infusion. Some degree of hemolysis is inevitable, because of binding of antibody-coated Rh-positive RBCs to phagocytes. The average decline in hemoglobin ranges from 0.5 to 1 g/dL. More significant intravascular hemolysis, hemoglobinemia/hemoglobinuria and acute renal failure have been reported in few (–0.1–1.5%) patients.

All these first-line therapies are compared in **Table 5** in terms of approximate response rate, time to recovery and adverse effects. Response to different therapies has been variably defined in previous studies. A recent classification has been proposed by IWG, which has been adapted by ASH (2011) for better and uniform reporting of response to different therapies in ITP and is presented in **Table 6**. Except in the rare situation of a life-threatening bleed, there is no indication for administering a combination of the first line drugs. Temptation for adding a second drug without giving adequate time for the response to occur following the first therapy should be avoided.

First-line Therapies for Persistent and Chronic Immune Thrombocytopenic Purpura

The goal of treatment for children with persistent or chronic ITP is to maintain a hemostatic platelet count with first-line therapies and to minimize the use of prolonged corticosteroid therapy. Approximately two-thirds of patients with ITP experience at least a short-term increase in platelets after receiving corticosteroids, IVIG, or IV anti-D. High-dose dexamethasone (20–28 mg/m²/day) and high-dose methylprednisolone (30 mg/kg/day for 3 days,

Table 5 First-line therapies for pediatric immune thrombocytopenic purpura

Therapy	Approximate response rate	Time to recover	Adverse events
IVIG (0.8–1 g/kg single dose)	>80% patients	1–2 days	Headache, fever, flu-like symptoms, aseptic meningitis
IV anti-D (50–75 µg/kg)	50–77%	1–2 days	Headache, fever, chills, rarely intravascular hemolysis and acute renal failure
Prednisolone 1–2 mg/kg/day x 14–21 days; 4 mg/kg/day x 7 days, taper and stop by D21; 2 mg/kg/day x 7 days, tapered and stopped by D21; 4 mg/kg/day x 4 days, no tapering	<75% patients depending on dose	2–7 days	Weight gain, gastritis, hypertension, mood changes, osteoporosis, cataract, glaucoma
Methylprednisolone 30 mg/kg/day (max 1 g/day) IV or PO x 3 days			

Table 6 Definitions of response to treatment of immune thrombocytopenic purpura

<i>Complete response (CR)</i>	A platelet count $\geq 100 \times 10^9/L$ measured on two occasions >7 days apart and the absence of bleeding.
<i>Response (R)</i>	A platelet count $\geq 30 \times 10^9/L$ and greater than twofold increase in platelet count from baseline measured on two occasions >7 days apart and the absence of bleeding.
<i>No response (NR)</i>	A platelet count $<30 \times 10^9/L$ or $<$ twofold increase in platelet count from baseline or the presence of bleeding. Platelet count must be measured on two occasions 24 hours apart.
<i>Loss of complete response</i>	A platelet count $<100 \times 10^9/L$ measured on two occasions more than 24 hours apart and/or the presence of bleeding.
<i>Loss of response</i>	A platelet count $<30 \times 10^9/L$ or a less than twofold increase in platelet count from baseline or the presence of bleeding. Platelet count must be measured on two occasions more than 24 hours apart.

Based on recommendations of the International Working Group 2009

followed by 20 mg/kg/day for 4 days) have been used in persistent and chronic ITP and reported to be effective in 60–80% patients. However, both are associated with worse side-effect profile compared with prednisolone.

High-dose Dexamethasone

The safety and efficacy of high-dose dexamethasone was evaluated in recent trials in adults as well as children with acute ITP. A recent multicenter Italian study (GIMEMA ITP Working group) evaluated dexamethasone administered in four cycles at 40 mg daily for 4 days every two weeks. Responses were seen in 85.6% (complete response in 64.5%, partial response in 20% and minimal response in 1.1%). The overall response rate was similar in children and adults [<18 years, 36/42 (85.7%); >18 years, 41/48 (85.4%)]. Similar results were reported by our prospective study in children with chronic ITP. Thirteen patients with severe/chronic ITP, who had received multiple platelet enhancing therapies previously, were given short-course high-dose dexamethasone (HDD-SC) (20 mg/m² IV daily for 4 days, four cycles repeated every 14 days). Complete response was observed in 66.6% and moderate response in 17% patients, whereas 17% patients had no response.

Periodic Doses of Intravenous Immunoglobulin and Anti-D

They may also be used as maintenance therapy to defer splenectomy in young children with chronic ITP. Low-dose, alternate-day prednisone therapy can be used as an adjunct to maintenance IVIG therapy. In Rh (D) positive patients with chronic ITP, periodic anti-D is preferred over IVIG because of ease of administration, comparable efficacy and lower cost.

Second-line Treatment Options in Immune Thrombocytopenic Purpura

Approximately 5% of all ITP patients either fail to respond to first-line therapies or their condition relapses following cessation of therapy. Second-line drug therapies include high-dose dexamethasone or methylprednisolone; high-dose IVIG or IV anti-D, which are useful for rapid elevation of platelet counts; vinca alkaloids, the immunosuppressants such as azathioprine,

and cyclosporine, danazol which are used in less urgent cases; and the anti-CD20 monoclonal antibody rituximab, a relatively new therapy for ITP patients for which safety and efficacy data are still emerging. Splenectomy has been shown to provide long-term efficacy, although safety issues remain a concern. With the development of effective noncytotoxic therapies for ITP, immunosuppressive approaches have become less popular. The ASH guidelines support rituximab or high-dose dexamethasone as a preferred second-line therapy, alternative to splenectomy.

Rituximab

Rituximab is a humanized monoclonal antibody directed against CD20, an antigen expressed on the surface of B lymphocytes but not present on most plasma cells. After binding to the CD20 antigen, the Fc-domain of rituximab facilitates B-cell lysis and rapid clearance of pre-B cells and B cells that lasts for 6–12 months. In addition, rituximab prevents the activity of Th1-autoreactive cells by increasing the number of regulatory T cells.

There are no randomized trials for rituximab in children with ITP, but in 4 cohort studies and 10 case reports, there is evidence that children with chronic ITP have an overall response rate of 61%. Lack of sustained response to rituximab in all patients is explained by persistence of autoreactive B cells in the germinal centers and the BM. In addition, the majority of plasma cells are preserved in patients receiving anti-CD20 Ab therapy. Recent ASH guidelines suggest use of rituximab for children or adolescents with ITP who have significant ongoing bleeding despite treatment with IVIG, anti-D, or conventional doses of corticosteroids and as an alternative to splenectomy in children and adolescents with chronic ITP or in patients who do not respond favorably to splenectomy. Several dosing regimens for rituximab have been described, but most of the children received 375 mg/m² weekly intravenous transfusions for four consecutive weeks. The safety of rituximab in chronic ITP patients has not been established and increased risk of reactivated viral infections (hepatitis B, cytomegalovirus and varicella zoster) is an important concern.

Splenectomy

Splenectomy has been recognized for nearly a century as being effective treatment for ITP. As a reticuloendothelial organ rich with Fc receptor-expressing phagocytes, the spleen is the major site wherein antibody-coated (opsonized) platelets are actively removed from the circulation. Thus, removal of the spleen leads to prolonged survival of opsonized platelets in the circulation. The spleen may also house plasma cells that produce antiplatelet antibodies; therefore, splenectomy may help eliminate the source of the errant autoantibodies as well that cause ITP. Splenectomy is definitive treatment for most children with ITP, raising their platelet counts to normal or at least to levels that support liberalization of physical activities. In one pediatric study, splenectomy resulted in significant platelet increase in 85% of patients with chronic ITP. The ASH suggests that splenectomy should be considered for patients with chronic or persistent ITP who have significant bleeding symptoms, intolerance of medical therapy, or the need for improved quality of life. With advances in surgery, laparoscopic splenectomy is considered safe, even in smaller children. However, bleeding is possible, particularly if platelet counts are less than $20 \times 10^9/L$ at the time of surgery. Nonetheless, some patients will fail to respond, and some initial responders may have recurrence of thrombocytopenia after splenectomy and some these relapses have been correlated with the presence of accessory spleens.

Splenectomized patients have lifelong enhanced risk of thrombosis and infection. The asplenic patients are at risk of *Haemophilus*, *Neisseria*, and pneumococcus sepsis and incidence of overwhelming sepsis postsplenectomy is on the order of 1–2%. Asplenic patients are also at heightened risk of certain protozoal

infections, especially malaria and babesiosis. As infectious risk is particularly high among very young children, many authorities advocate deferring splenectomy until a minimum of 5 years of age. Immunization against *Haemophilus influenzae* type B, *Meningococcus*, and pneumococcus is recommended preoperatively, and oral prophylactic antibiotic therapy (typically penicillin) is recommended postoperatively, as is appropriate sepsis evaluation for fever. Portal vein thrombosis in the immediate postoperative period has also been reported in children.

Immunosuppressive Agents

A number of immunosuppressive agents other than steroids have been used to treat refractory ITP. These drugs are compared in **Table 7** in terms of doses, response rates and adverse effect profile.

Newer and Emerging Therapeutic Agents

Recombinant Thrombopoietin and Thrombopoietin-Receptor Agonists

An important advancement in the management of ITP is the introduction of TPO receptor agonists. The impact of this discovery has been just as important for the advancement of current understanding of pathophysiology, as it has been for expanding treatment options for patients with refractory disease. With increasing evidence that platelet production may be impaired in ITP, factors that stimulate the proliferation, survival, and differentiation of megakaryocytes have become potential therapeutic agents. Several TPO receptor agonists have been studied. The first were recombinant forms of human TPO, but development of these

Table 7 Immunosuppressive agents used in immune thrombocytopenic purpura

Drug	Mechanism of action	Dose	Response rate	Adverse effects	Important points to remember
Azathioprine	Acts on lymphocytes	50–200 mg/m ² /day orally, combination with steroids synergistic and allow steroid dose reduction	Approx 45%	Dose-related leukopenia, opportunistic infections, malignancy	Continuous therapy for 4–6 months is required before a patient is considered unresponsive
Cyclophosphamide	Alkylating agent, acts on lymphocytes	Oral: 1–2 mg/kg/day × 16 weeks IV: 0.3–1 g/m ² 1–3 doses every 2–4 weeks	24% to 85%	Myelosuppression, alopecia, nausea, infertility, teratogenicity, hemorrhagic cystitis and increased risk for malignancy	Used for patients refractory to corticosteroids and/or splenectomy
Cyclosporin A	Disrupts T-cell function through calcineurin inhibition	5 mg/kg/day divided oral doses, (maintaining a serum cyclosporine level of 200–400 ng/mL)	>80% of patients resistant to 1st line therapy, 42% complete response	Fatigue, renal insufficiency, hypertension, hirsutism and liver dysfunction	The drug should be discontinued if no response after 4 weeks
Tacrolimus	Disrupts T-cell function through calcineurin inhibition	0.15–0.3 mg/kg/day in divided oral doses (maintain trough serum concentration of 5–20 ng/mL)		Hypertension, tremors, headache and hyperglycemia	
Danazol	Attenuated androgen, unknown mechanism in ITP	Orally 300–400 mg/m ² /day, in divided doses (10–15 mg/kg/day)	60–67%	Acne, hirsutism, fluid retention, deepening of voice in women, headache, nausea, rash, breast tenderness and irregular menstrual bleeding	Two months therapy is required before a response is seen. Older females and splenectomized patients have the highest response rate
Dapsone	Moderate steroid-sparing agent	Orally at a dose of 75–100 mg/day		Male patients at risk for G-6-PD deficiency should be screened before starting treatment, monitor for hemolysis and methemoglobinemia	Splenectomized patients have a low response rate
Mycophenolate mofetil	Antiproliferative immune-suppressant, inhibits both T- and B-cells	Progressively increasing doses (250 to optimally 1,000 mg/day twice a week over 3 weeks)	Approx. 39% in refractory ITP	Generally well tolerated	Effective in steroid-resistant ITP patients
Vinca alkaloids (Vincristine and vinblastine)	Bind tubulin and inhibit microtubule polymerization, disrupt phagocytosis	Vincristine: 1.5 mg/m ² (max 2 mg), vinblastine 6 mg/m ² (max. 10 mg) IV weekly	Approx. 47%	Vincristine-peripheral neuropathy, constipation and alopecia. Vinblastine-dose related myelosuppression	A 4-week trial is required, before considering the drug ineffective
Interferon Alpha	Unknown mechanism of action	3 million U/m ² subcutaneous thrice a week for 4 weeks	25% in chronic, refractory adult ITP	Flu-like symptoms and neutropenia	Not tested in children

agents was halted after one form caused thrombocytopenia due to autoimmune destruction of endogenous TPO in several patients. The so-called second-generation thrombopoietic growth factors have been designed to avoid antigenicity. A number of studies with recombinant TPO and TPO receptor agonists have shown encouraging results in adults, and following two synthetic TPO molecules are now licensed for treatment of severe chronic adult ITP.

Romiplostim (AMG 531)

Romiplostim has been FDA-approved since 2008, and the majority of patients have had a very good response with an initial dose of 1 µg/kg given subcutaneously weekly. Two randomized studies investigating romiplostim reported an increase of the platelet count to over $50 \times 10^9/L$ in more than 80% of the children. The platelet response was maintained for a median of 7 weeks and romiplostim seemed to be safe. Further studies in children are definitely needed, but initial results suggest that romiplostim may have a role in the treatment of severe chronic ITP in children.

Eltrombopag

A phase 2 study in chronic ITP patients provides evidence that eltrombopag can both increase platelet count and possibly reduce bleeding symptoms. Another recent open label study evaluated the safety and efficacy of eltrombopag in adults. Both splenectomized and nonsplenectomized patients achieved platelets $>50 \times 10^9/L$ at least once (80% and 88%, respectively) in this study. Long-term treatment with eltrombopag was reported safe, well tolerated, and effective in maintaining platelet counts in the desired range. Increased risk for thrombosis, rebound thrombocytopenia and formation of BM reticulin are potential safety concerns being evaluated with use of TPO receptor agonists.

Rozrolimupab

Rozrolimupab is a recombinant mixture of 25 fully human Rh D-specific monoclonal antibodies, represents a new class of recombinant human antibody mixtures. In a recent dose escalation study, 61 RhD+ adult patients with primary immune thrombocytopenia received a single intravenous dose of rozrolimupab ranging from 75 µg/kg to 300 µg/kg. At the dose of 300 µg/kg platelet responses were observed after 72 hours and persisted for at least 7 days in 8 of 13 (62%) patients. The most common adverse events were headache (20%) and pyrexia (13%). Rozrolimupab was well tolerated, but yet to be tested in pediatric patients.

Emergency Treatment in Immune Thrombocytopenic Purpura

Emergency treatment is required for severe, life-threatening bleeds, e.g., ICH or organ-threatening bleeds. The aim of treatment is to control the bleeding and salvaging the organ as early as possible. This can be achieved with following measures:

First-line Therapies in Combination

High-dose methylprednisolone is administered in combination with IVIG or anti-D. IVIG and methylprednisolone may be repeated for at least 1–2 days, based on response.

Platelet Transfusions

Transfusions are indicated in the setting of life-threatening bleeds to buy time for drug therapy to have an action. At least 2–3 fold higher dose of platelets is administered to temporarily increase the circulating platelet count. Survival of transfused platelets may be improved with concurrent IVIG therapy. Continuous infusion of platelets may be beneficial in selected cases.

Splenic Artery Embolization or Splenectomy

Splenic artery embolization or emergency splenectomy is indicated in life-threatening bleeds unresponsive to first-line drugs or in a patient who is acutely ill and will benefit from an immediate rise in platelet count. Splenic artery embolization is typically performed by interventional radiologist and may be life-saving. The splenic artery is cannulated through the femoral artery and polyvinyl alcohol particles, coils or gelatin sponges are utilized for embolization. There is often a prompt rise in platelet count, as in splenectomy. However, the infarcted spleen has to be surgically removed within the next few days to avoid complications of pain and fever. If expertise is available, splenic artery embolization is a faster and safer bridge procedure prior to splenectomy. Data regarding the use of splenic artery embolization in ITP related life-threatening bleeds is limited and availability of expertise is a major limitation.

Emergency Splenectomy

It is indicated if facilities for splenic artery embolization are not available. Despite first-line therapies, several patients still have very low platelet count at the time of splenectomy. The feasibility and safety of laparoscopic splenectomy in patients with severe thrombocytopenia has been reported, hence, emergency splenectomy should not be delayed in view of severe thrombocytopenia.

Recombinant Vlla

It has been used in ICH refractory to platelet enhancing agents as *off-label use*. It is used in a dose of 90–120 µg/kg infusions every 2–3 hourly, till the cessation of bleeding.

Adjunctive Therapies

Control of bleeding from mucosal surfaces, particularly epistaxis, gum bleeding and menorrhagia can be aided with antifibrinolytic agents. Two agents, aminocaproic acid and tranexamic acid are available. Tranexamic acid is preferred due to longer half-life, higher potency and lower toxicity. Tranexamic acid is given in a dose of 25–50 mg/kg every 6–8 hours. It is absorbed from the buccal mucosa and subsequently secreted in the saliva. Hence, in oral bleeding, hemostasis is better achieved with a mouthwash or local application of crushed tablets in younger children. Aminocaproic acid is administered as 100–200 mg/kg (maximum 10 g) stat, followed by 50–100 mg/kg/dose every 6 hourly (maximum 5 g). This supportive therapy is safe, cheap and effective. Antifibrinolytic agents are contraindicated in hematuria, as ureteric clot formation can result in colic and obstruction of urine outflow.

Site-Specific Management of Bleeds

Epistaxis

Caretakers should be educated regarding the simple maneuver of nasal pinching. Sustained pressure should be applied by pinching the soft part of the nose below the nasal bones, on the ala nasi, which corresponds to Kiesselbach plexus (Little's area), between the thumb and index finger for 20 minutes, continuously. Nasal packing should be done if bleeding persists for more than 20 min with continuous digital pressure, besides starting first-line drugs.

Menorrhagia

Menorrhagia in an adolescent with ITP is commonly managed with oral contraceptive pills containing estrogen and progesterone (levonorgestrel) or cyclic high-dose progestins, e.g., norethisterone. If unresponsive, GnRH agonists, including leuprolide can be used for short period, as this group of drugs has adverse effect on bone mineral density, besides being expensive. Severe acute bleeding will require therapy with intravenous estrogens and platelet enhancing

drugs. Supportive management with tranexamic acid and iron supplementation is important. Nonsteroidal anti-inflammatory drugs (NSAIDs), including mefenamic acid and intramuscular injections (e.g., depot medroxyprogesterone acetate) should be avoided.

Intracranial Hemorrhage

Intracranial hemorrhage should be managed in an intensive care unit with maintenance of airway, breathing and circulation; head end elevation (30°) and osmotherapy (mannitol or 3% saline) for raised intracranial pressure. Neurosurgery consultation should be sought for definitive management. Besides these, emergency measures to raise the platelet counts at hemostatic levels should be initiated.

Supportive Care

One of the most challenging aspects to the management of a child with ITP is restricting participation in normal play and sports activities because of concerns over bleeding risk. In cases where the ITP persists for weeks or months, activity limitations must be balanced with an appreciation of the consequences of *sheltering* a child with chronic ITP, including weight gain and sick child syndrome. Participation in any activity associated with a significant risk of trauma (especially head injury) should be avoided when platelet counts fall below 50×10^9 to $75 \times 10^9/L$. This includes avoiding stairs and other climbing structures such as playground equipment for younger children, and avoiding contact sports for older children and adolescents. Safety gears including helmets, knee pads, etc. should be used for outdoor play and cycling. Regardless of approach, medications that inhibit platelet function, most notably NSAIDs and aspirin, and intramuscular injections should be avoided.

Vaccination for Children with Immune Thrombocytopenic Purpura

Children may develop ITP after vaccinations with a live attenuated vaccine. However, the incidence of ITP is significantly lower than that observed during the natural diseases that the vaccine prevents. Consequently, vaccination is not contraindicated in children with a history of ITP. Hence, ASH 2011 guidelines recommend that children with a history of ITP who are unimmunized receive their scheduled first MMR vaccine. In children with either nonvaccine or vaccine-related ITP who have already received their first dose of MMR vaccine, vaccine titers can be checked. If the child displays full immunity (90–95%), then no further MMR vaccine should be given. If the child does not have adequate immunity, then the child should be reimmunized with MMR vaccine at the recommended age.

PROGNOSIS

The outcome of children with ITP is generally good. Most cases have only skin bleeds. Severe bleeding manifestations are described in 3–5% cases. With appropriate therapy, most cases with severe bleeding recover. Complete remission with or without drug therapy occurs in 60–70% cases within initial few months from diagnosis. According to ICIS observations, incidence of chronic ITP is higher than generally reported figure of 10%. However, large majority of them achieve remission in second year of their illness.

IN A NUTSHELL

1. Immune thrombocytopenic purpura is a self-limiting disorder and most children (70–80%) undergo spontaneous remission over a period of 6 months.
2. Skin and other minor bleeds do not need any specific platelet raising therapy, irrespective of the platelet count.
3. There is a small but definite risk of ICH (~0.2%) which persists till the resolution of thrombocytopenia. Treatment has not been proven to reduce the incidence of ICH, nor does it reduce the chances of progression to chronic ITP.
4. Corticosteroids, IVIG and IV anti-D, are the first-line therapy for ITP. Second-line treatment options include rituximab, high-dose dexamethasone, splenectomy and immunosuppressive agents.
5. Routine transfusion of platelets is not required as transfused platelets are also destroyed by circulating antiplatelet antibodies.
6. Supportive therapy (i.e., fibrinolytic agents and local care) plays as important role as the main therapy in management of ITP.
7. To avoid trauma, particularly head injury, use of helmets during outdoor play, cycling, etc. should be advised. NSAIDs (aspirin, ibuprofen, etc.) and intramuscular injections should be avoided.
8. Patient should be brought to physician's notice in case of headache, hematuria or GI bleed, as it is an indication for systemic therapy.

MORE ON THIS TOPIC

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Chapter 38.21

Platelet Function Defects

Neelam Varma

Platelet function defects (PFDs) are a heterogeneous group of rare diseases. The degree of functional abnormality of platelets and thrombocytopenia determines the clinical manifestations. PFDs are important, as severe defects may cause excessive bleeding beginning in early childhood, although most of PFDs have mild bleeding tendencies which present late and therefore it is not always easy to make distinction among inherited and acquired quantitative and qualitative platelet disorders.

However in clinical practice, most of the platelet disorders are due to acquired factors including drugs and metabolic diseases. The diagnosis of PFD requires extensive laboratory investigation. Routine laboratory tests are not satisfactory for differential diagnosis in some cases, and most of the specific tests are not readily available. Although PFDs are rare, elucidation of their pathogenesis has contributed enormously to current knowledge. The identification of molecular pathology in patients with PFD has improved our understanding of normal megakaryocyte and platelet physiology, as well as the mechanisms of hemostasis and thrombosis.

EPIDEMIOLOGY

Population prevalence is estimated to be approximately 1 in 1,000,000 for Glanzmann thrombasthenia (GT) and Bernard-Soulier syndrome (BSS) and 1 in 40,000 for nonsevere hereditary platelet function defects (HPFD), although nonsevere HPFD may be underrecognized in most clinical diagnostic centers.

Accurate diagnosis of the severe phenotype disorders like BSS and GT is essential in order to direct specific treatments, to provide accurate prognostic advice and for genetic counseling. To fulfil these objectives, it is necessary to identify both the functional platelet defect at protein level and the causative genetic variation(s).

Quantitative and qualitative integrity of platelets can be checked by screening tests like platelet count, skin bleeding time or platelet-vWF function analyzer-100 (PEA-100) tests. However, these tests underestimate some platelet disorders. In the setting of suggestive clinical/family history and normal vWF function, further tests should be planned.

PATHOGENESIS

Classification of inherited platelet disorders based on platelet count, size, function, or underlying genetic abnormality is depicted in **Table 1**. Both quantitative and qualitative abnormalities of platelets lead to signs and symptoms suggestive of defects of primary hemostasis, i.e., mucocutaneous bleeds, epistaxis, menorrhagia, and small ecchymoses over skin.

It is rare for patients to present with spontaneous life-threatening bleeding (e.g., intracranial hemorrhage, massive gastrointestinal or genitourinary bleeding). Menorrhagia and bleeding during pregnancy and labor are a problem in female patients. Unexpected excessive bleeding after trauma or surgery may be the first symptom in milder cases of PFD. Rarely, PFD is a part of a complex of multisystem disorder such as Fanconi anemia, Chediak-Higashi syndrome, or May-Hegglin anomaly (**Table 1**). Platelet count, size and morphology must be assessed before embarking upon further investigations. *Low platelet count* must always be cross-checked by examination of a peripheral blood film. Platelet aggregates and platelet satellitism (binding to neutrophils) induced by ethylenediaminetetraacetic acid or agglutinins, can

Table 1 Classification of inherited platelet disorders

1. Decreased production of platelets
 - a. CAMT
 - b. Congenital hypo/amegakaryocytic thrombocytopenia with skeletal abnormalities
 - i. TAR syndrome
 - ii. ATRUS
 - iii. Fanconi anemia
2. MYH9-related diseases:
 - a. May-Hegglin anomaly
 - b. Epstein syndrome
 - c. Fechtner syndrome
 - d. Sebastian syndrome
3. Platelet membrane phospholipid abnormalities:
 - a. Scott syndrome
 - b. Stormorken syndrome
4. Platelet granule deficiencies (storage pool disease)
 - a. α -granule defects:
 - i. Gray platelet syndrome
 - ii. Paris-Trousseau syndrome
 - iii. Quebec platelet syndrome
 - iv. ARC syndrome
 - b. Dense granule defects:
 - i. Hermansky-Pudlak syndrome
 - ii. Chediak-Higashi syndrome
 - iii. Griscelli syndrome
 - c. α - and dense-granule defects
5. Disorders of platelet surface receptors
 - a. GP Ib-IX-V defects
 - i. Bernard-Soulier syndrome
 - ii. Platelet-type vWD
 - iii. Velocardiofacial syndrome
 - b. Integrin $\alpha_2\beta_3$ (GP IIb-IIIa) defects: Glanzmann thrombasthenia
 - c. GPVI defects
 - d. Integrin $\alpha_2\beta_1$ (GP Ia/IIa) defects
 - e. Integrin $\alpha_5\beta_1$ (VLA-5) defects
 - f. Integrin $\alpha_6\beta_1$ (VLA-6) defects
 - g. Integrin $\alpha_v\beta_3$ defects
6. *Miscellaneous*: GATA-1 related thrombocytopenia, Wiskott-Aldrich syndrome, mediterranean macrothrombocytopenia, Montreal platelet syndrome, familial platelet disorder with propensity to myeloid malignancy (FDP/AML)

Abbreviations: CAMT, congenital amegakaryocytic thrombocytopenia; TAR, thrombocytopenia with absent radius; MYH9, mutations of nonmuscle heavy chain gene; vWD, von Willebrand disease; GP, glycoprotein

easily be detected as a cause of pseudothrombocytopenia. Large platelets are found in BSS and increased peripheral platelet destruction; gray vacuolated platelets in α -granule deficiency and microplatelets in Wiskott-Aldrich syndrome.

APPROACH TO DIAGNOSIS

When to Suspect

Platelet function defects should be suspected whenever there is bleeding with normal platelet count or when the bleeding is disproportionate to the severity of thrombocytopenia. Positive family history of platelet type bleeding with normal platelet count and presence of congenital malformations/physical stigmata indicate toward PFD. The following points should be evaluated:

- Family history for consanguinity, bleeding in family members/siblings
- Type and severity of bleeding [questionnaire-based bleeding assessment tools (BATs)]
- Platelet count determination

- Exclusion of drugs—nonsteroidal anti-inflammatory drugs (NSAIDs), secondary causes such as uremia, liver disease
- Examination of platelet morphology:
 - Giant platelets
 - Inclusions within neutrophils
 - Absence of platelet clumps on peripheral blood smear
 - Gray platelets.
- *Clot retraction test*: Useful in GT and fibrinogen disorders
- *Platelet-vWF function analyzer-100 (if available for screening)*: Measures closure time of aperture in collagen/epinephrine or collagen/adenosine 5'-diphosphate (ADP) cartridges at high shear rates.
- Platelet aggregometry on platelet rich plasma (PRP) with agonists. Commonly used agonists are: (1) epinephrine; (2) ADP; (3) collagen; (4) thrombin; (5) arachidonic acid; (6) low (< 0.4 mg) and high-dose ristocetin.

Pre-requisites for Platelet Function Testing

- Stop aspirin/NSAIDs for minimum 7 days
- Platelet count has to be greater than $100 \times 10^9/L$.
- Fasting sample and a normal control sample are required.

Characteristic Findings

- *Bernard-Soulier syndrome* Absence of aggregation with ristocetin and normal aggregation with other agonists. Not corrected on testing after mixing with normal pooled plasma (NPP).
- *Glanzmann thrombasthenia* Absence of aggregation with epinephrine, ADP, collagen and arachidonic acid. Aggregation-disaggregation response can be seen with ristocetin.
- *Disorders of granule secretion/storage pool defect* Show absence of secondary wave of aggregation.

Investigations

- *Flow cytometry (FCM)* To confirm deficiency of platelet membrane glycoproteins. Platelet aggregation studies can also be performed with FCM.
 - *Electron microscopy (EM)* In cases of deficiency of alpha/delta granules.
- Platelet function tests (PFTs) are listed in **Table 2**.

Bleeding Time

Bleeding time is a poor predictor of platelet dysfunction and bleeding complications. The test involves making a superficial skin incision on the patient's forearm using a standardized device and the blood from the wound is blotted intermittently until the bleeding stops. The time taken from the incision to cessation of bleeding (formation of hemostatic plugs) is noted as bleeding time. It depends upon the platelet count and the ability of platelets to adhere to subendothelium and form aggregates. Prolonged bleeding time is observed in patients with thrombocytopenia, platelet function disorders, von Willebrand disease (vWD), vascular abnormalities and rarely severe deficiency of factors V/XI/fibrinogen.

Bleeding time has many confounders, is poorly reproducible and difficult to standardize. Presently, it has been mostly discontinued in clinical practice and is replaced by other simpler screening tests.

Platelet Function Analyzer-100

This is a rapid whole blood analyzer capable of screening for PFT. Whole blood is passed through a hole in a membrane coated with collagen and ADP (CADP) or collagen and epinephrine (CEPI). Under the combined effects of high shear rates and vWF, platelets when encountered with the membrane spontaneously adhere to collagen and aggregate due to stimulation by ADP or epinephrine.

Table 2 Platelet function tests

Test	Remarks
1. Adhesion tests <ul style="list-style-type: none"> • Retention in a glass bead column • Baumgartner technique • PFA-100 	Good screening test
2. Aggregation tests <ul style="list-style-type: none"> • Turbidometric technique using ADP. Collagen, ristocetin, adrenaline, thrombin, arachidonic acid, endoperoxide analogs, calcium ionophores 	Gold standard test
3. Tests of granular content and release <ul style="list-style-type: none"> Dense bodies <ul style="list-style-type: none"> • Electron microscopy • ADP and ATP content (bioluminescence)* • Serotonin release* Granules <ul style="list-style-type: none"> • B-thromboglobulin** • Platelet factor 4** • vWF • Fluorescence by flow cytometry 	*Best measured in a specialist laboratory **Radioimmunoassay kits have problems of reproducibility and result interpretation
4. Prostaglandin pathways <ul style="list-style-type: none"> • TXB2 radioimmunoassay 	Quantitation by radioimmunoassay
5. Platelet procoagulant activity <ul style="list-style-type: none"> • Prothrombin consumption index 	Rarely performed, indicates completion of membrane flip-flop
6. Flow cytometry <ul style="list-style-type: none"> • Glycoprotein surface expression* • Activation • P-selectin (CD-62) surface expression • Fibrinogen binding • Annexin binding to phosphatidyl serine** • Conformational change in IIb/IIIa • Platelet granule fluorescence 	*May not correlate with function **Indicates completion of membrane flip-flop

Abbreviations: ADP, adenosine 5'-diphosphate; ATP, adenosine 5'-triphosphate; PFA-100, platelet-vWF function analyzer-100

The time taken for a platelet plug to form, occlude the aperture and stop the flow of blood is measured as closure time (CT). Markedly prolonged PFA-100 CT is observed in GT and BSS and IIb/IIIa glycoprotein receptor inhibitors (abciximab, tirofiban, etc.). More severe types of vWD (types 2 and 3) are easily detected by PFA-100. Sensitivity is quite low for mild-to-moderate bleeding disorders like storage pool disease and secretion defects.

Platelet-vWF function analyzer-100 CT can be affected by hematological variables unrelated to platelet function. Severe thrombocytopenia (platelet count < $50 \times 10^9/L$) and anemia (hematocrit < 25%) result in abnormally prolonged CT. PFA-100 CT also is prolonged in patients with vWD and in normal O blood group individuals (known to have low vWF levels).

Platelet Aggregometry

Two methods using different blood preparations are practiced for study of platelet aggregation: PRP by optical method or whole blood by impedance method.

Platelet Rich Plasma Aggregation by Optical Method

The patient and control individuals should not ingest any drugs, food items or beverages that are known to affect aggregation for a minimum of 10 days. Overnight fasting is advisable as presence of chylomicrons may disturb aggregation patterns. Panel comprises of following agonists:

- **Adenosine 5'-diphosphate** Low concentrations of ADP (< 0.5–2.5 $\mu\text{mol/L}$) cause primary or reversible aggregation. Higher concentrations lead to secondary or irreversible aggregation.
- **Collagen** Lower concentrations cause a short *lag* phase succeeded by a single wave of aggregation resulting from activation of arachidonic acid pathway and release from granules. Higher concentrations cause a sudden increase in intraplatelet calcium concentration and may lead to release reaction without activating the prostaglandin pathway.
- **Ristocetin** This agonist does not cause aggregation but induces platelet *agglutination* by binding to vWF and membrane receptor.
- **Arachidonic acid** This agonist induces thromboxane A₂ (TXA₂) generation and granule release even if there is a defect of agonist binding to the surface membrane or of the phospholipase-induced release of endogenous arachidonate. When further steps in the pathway are impaired such as absence or inhibition of cyclooxygenase (aspirin effect), arachidonic acid does not produce normal aggregation response.
- **Epinephrine/adrenaline** Its response resembles that of ADP; however, aggregation is not preceded by shape change. Severely reduced response to epinephrine may be shown by some clinically normal persons.

It is a gold standard test for platelet function, but is time-consuming, labor intensive and requires adequate expertise in technical procedure and interpretation. Results are modified by lipemia, hemolysis or red-cell contamination. All these factors cause lot of interlaboratory variability in aggregometry interpretation.

Whole Blood Aggregation by Impedance Method

This is a simple and fast method which obviates the need of preparing PRP. Impedance method is thought to be more sensitive in the study of hyperactive platelets and effects of aspirin and clopidogrel on platelets. An aggregation curve is generated, resistance to the electric flow being proportional to platelet aggregation. Reduced or absent aggregation response to one or more agonists clinches the diagnosis or provides important leads (**Table 3**).

Platelet Secretion Assays

Platelet secretion can be measured by luciferin-luciferase assay (easy to perform) and ¹⁴C-labeled serotonin release assay.

Platelet Flow Cytometry

Flow cytometer is a very sensitive tool to assess the expression of glycoprotein (or other molecules) on the platelets. In expert hands, it finds use in diagnosis of following conditions: Bernard-Soulier syndrome, GT, acquired GT (multiple monoclonal antibodies used to detect autoantibody blockade of GP IIb/IIIa), storage pool defect, heparin-induced thrombocytopenia, platelet activation and reactivity, and monitoring thrombopoiesis.

Platelet function disorders are a rare and underestimated cause of bleeding in hematological practice. The inherited variety includes defects in platelet adhesion, aggregation, secretion and platelet procoagulant activities. Affected individuals seek medical opinion depending upon personal perception of seriousness of the bleeding manifestations. Milder phenotypes may pass off unrecognized in childhood and may even be missed later in life, unless specially tested for PFT. Many mild platelet function disorders in females present as menorrhagia. Plan of investigations includes a coagulation screen, which may show a prolonged bleeding time, followed by platelet aggregation tests with a panel of agonists. Flow cytometry for platelet surface markers, membrane glycoprotein analysis and identification of the genetic defects must be done later. Extra care should be taken while drawing the venous blood, preparation of samples, and interpretation of results of PFT.

MANAGEMENT

The majority of patients with PFD do not need treatment on a regular basis, but require it after injury, during surgical procedures, and during bleeding episodes. Patients have to be educated about maintaining dental hygiene, avoiding contact sports and activities carrying bleeding risk, and avoiding the use of antiplatelet drugs. Bleeding from minor cuts, nose, and gingiva can be stopped by applying pressure. Minor bleeding symptoms can be decreased by using topical hemostatic agents such as gelatin sponges, fibrin sealants, and antifibrinolytic drugs such as tranexamic acid.

The data on the efficacy and safety of desmopressin [1-desamino-8-D-arginine vasopressin (DDAVP)] in the treatment of intermittent peritoneal dialysis (IPD) patients are limited because the literature includes only small case series with different

Table 3 Comparative results of platelet aggregometry and PFA-100

Disorder	Platelet aggregation					PFA-100 CT		Remarks/further tests
	ADP/epinep		Col	AA	Ri	CADP	CEPI	
	1 ^o	2 ^o						
Inherited								
vWD	N	N	N	N	a/d/i	P	P	Assay vWF-ag and RiCoF
GT	a	a	a	a	N	P	P	GP IIb/IIIa expression
BS	N	N	N	N	a	P	P	Large size; low platelet count; GP Ib expression
SPD	N/d	a	N/d	N/d	N	N/P	N/P	ATP/ADP pool
Acquired								
Aspirin	N/d	a	D	a	N	N	P	Stop drug and retest
ADP-RA	d	d	N/a	N	N/a	N/P	N/P	
GP IIb/IIIa inh	d	d	D	a	N/a	P	P	

1⁰ = primary wave, 2⁰ = secondary wave

Abbreviations: a, absent; ADP-RA, ADP receptor antagonists; BS, Bernard-Soulier syndrome; CT, closure time; d, decreased; GPIIb/IIIa inh, GPIIb/IIIa inhibitors; GT, Glanzmann thrombasthenia; i, increased; N, normal; P, prolonged; SPD, Storage pool disease; vWD, von Willebrand disease

results. Desmopressin is indicated for the prevention or treatment of bleeding episodes in patients with type-1 VWD and in patients with hemophilia A with factor VIII levels >2–5%. It stimulates the release of vWF from endothelial cells and increases factor VIII levels in plasma.

Both gynecologic and hematologic treatments are required for management of menorrhagia in patients with PFD. Oral contraceptives or hormonal intrauterine devices along with tranexamic acid can be used to reduce bleeding during menses. Patients with severe bleeding after trauma, surgery, or delivery may require platelet and RBC transfusions.

MORE ON THIS TOPIC

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IN A NUTSHELL

1. Severe platelet function defects can present early in childhood with bleeding manifestations.
2. Signs and symptoms suggestive of defects of primary hemostasis can be caused by both quantitative and qualitative abnormalities of platelets.
3. Platelet count, size and morphology must be assessed before performing further investigations.
4. Further tests should be planned in the setting of suggestive clinical/family history and normal vWF function.
5. Platelet-vWF function analyzer-100 is a rapid whole blood analyzer capable of screening for PFT, however currently not available in India.
6. Platelet aggregometry is the gold standard test for platelet functions and provides direction for planning further tests.
7. Platelet FCM, if expertise and equipment are available, can be conveniently used for investigation of specific disease entities like BSS, GT, etc.
8. Adequate care must be taken for giving instructions to the patient and controls to avoid ingestion of items likely to interfere with platelet aggregation, drawing the venous blood, and preparation of samples.
9. Abnormal results of PFT should be interpreted carefully and repeated at least once.

Chapter 38.22

Thrombotic Disorders

Sidharth Totadri, Deepak Bansal, RK Marwaha

With increasing clinical awareness and availability of imaging modalities, pediatric thrombotic conditions are being increasingly diagnosed and treated. Prothrombotic states, which may be primary or secondary, include venous thromboembolic events, arterial thrombosis, arterial ischemic stroke and cerebral venous sinus thrombosis. Advances in the field of anticoagulant therapy have made it possible to reduce the morbidity and mortality resulting from these conditions.

EPIDEMIOLOGY

Data available from international registries and databases suggest that thromboembolic events have increased fivefold to tenfold, from 5 per 10,000 to 18–58 per 10,000 hospitalized children, over the past 20 years. This increased incidence may be attributed to the advances in neonatology and pediatric medicine. There has been progress in neonatal care and survival of preterm and low birth weight babies who have a physiological hypercoagulable state. There is improvement in critical care of sick children and extensive use of central venous access devices, which are the most common cause of pediatric thrombosis. There has been increased treatment and survival of children with chronic illnesses, including nephrotic syndrome, lupus and cancers. Progress in radiology and availability of modalities, including Doppler, computed tomography (CT) and magnetic resonance imaging (MRI), has led to increased diagnosis of thromboembolic events. There is increased awareness and screening for inherited thrombophilic states and antiphospholipid antibody syndrome.

PATHOPHYSIOLOGY

The pathological tendency to develop excessive and unwanted thrombosis is called thrombophilia. This may be the result of inherited genetic changes involving the physiological anticoagulant proteins, or secondary to acquired risk factors. The normal anticoagulant mechanism is illustrated in **Figure 1**. The tissue factor initiated extrinsic pathway and the surface dependent intrinsic pathway converge to produce thrombin from prothrombin. This is regulated by dynamic inhibitory systems. Protein C is activated by the thrombin-thrombomodulin complex, leading to inactivation of factors Va and VIIIa. This action is catalyzed by protein S. Antithrombin, which is present in the normal plasma, neutralizes the procoagulant serine proteases, namely, factors XIa, IXa, Xa and IIa. Tissue factor (TF) pathway inhibitor blocks the TF-factor VIIa complex.

Inherited Thrombophilias

Inherited mutations affecting the proteins involved in anticoagulant mechanisms may lead to unregulated production of thrombin in inappropriate locations. The common inherited thrombophilias are summarized in **Table 1**.

Protein C and Protein S Deficiency

Hereditary deficiency of protein C or S may be homozygous, heterozygous or compound heterozygous. Compound heterozygous or homozygous deficiencies manifest in the first few days of life as life threatening disseminated intravascular coagulation and purpura fulminans. Purpuric lesions form on pressure points and progress into painful black eschars. There is

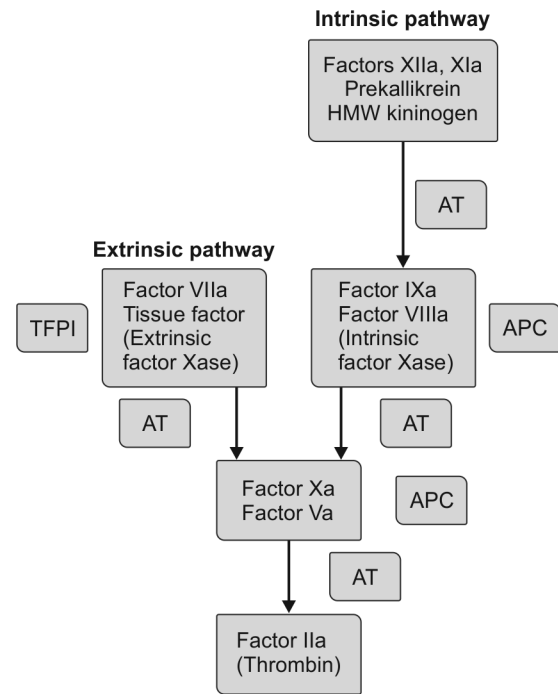


Figure 1 Coagulant and anticoagulant factors in the normal physiological pathway. Antithrombin (AT) inhibits activated factors XI, IX, X and thrombin. Activated Protein C (APC) in conjunction with Protein S inhibits activated factor V and VIII. Tissue factor protein inhibitor (TFPI) inhibits the extrinsic pathway

increased risk of recurrent thromboembolic phenomena in older children and adolescents, such as deep vein thrombosis (DVT) of lower extremities and pulmonary embolism (PE). Severe deficiency states are diagnosed by protein activity of less than 1% on clotting or immunological assays. Heterozygous states need repeat assay after 6 months, as there may be a false decrease in protein levels during the thrombotic episode secondary to consumption.

Homozygous/compound heterozygous patients require fresh frozen plasma 10–20 mL/kg or protein C concentrate, twice daily, till resolution of the purpuric lesions followed by lifelong anticoagulation with low molecular weight heparin (LMWH) or warfarin to prevent thrombosis.

Antithrombin Deficiency

This condition also manifests with thromboembolic disease, most commonly DVT and PE. The risk increases with age; the presentation being uncommon before puberty. In some patients, functional deficiency with mutation affecting the heparin binding site may make them refractory to conventional doses of heparin.

Table 1 Inherited thrombophilic conditions

Condition	Inheritance
Antithrombin deficiency	AD
Protein C deficiency	AD
Protein S deficiency	AD
Factor V Leiden mutation	AD
Prothrombin G20210A	AD
MTHFR mutations	AR
Dysfibrinogenemias	AD

Abbreviations: MTHFR, Methylene tetrahydrofolate reductase; AD, autosomal dominant; AR, autosomal recessive

Factor V Leiden and Prothrombin G20210A Mutations

These are point mutations, which respectively render factor V and II resistant to protein C induced inactivation, causing a hypercoagulable state. There is predisposition to venous thromboembolism (VTE). They can be diagnosed by polymerase chain reaction for the specific mutations.

Methylenetetrahydrofolate Reductase Mutations

Mutations affecting the methylenetetrahydrofolate reductase (MTHFR) enzyme (e.g., *MTHFR* C677T) results in hyperhomocysteinemia, which in turn leads to endovascular dysfunction and thrombophilia. Hyperhomocysteinemia is an independent risk factor for VTE, cerebral venous sinus thrombosis and arterial ischemic stroke. Diagnosis is suspected by elevated fasting homocysteine levels. Folate supplementation can decrease the risk of thrombotic events.

Acquired Thrombophilic States

The classical Virchow's triad of thrombosis includes: (1) stasis, (2) hypercoagulable state, (3) endothelial injury. Acquired thrombophilic states induce one or more of these components. The pathophysiology of these conditions is outlined in **Figure 2** and **Table 2**. **Figure 3** exemplifies an acquired thrombophilic state in a patient with thalassemia major.

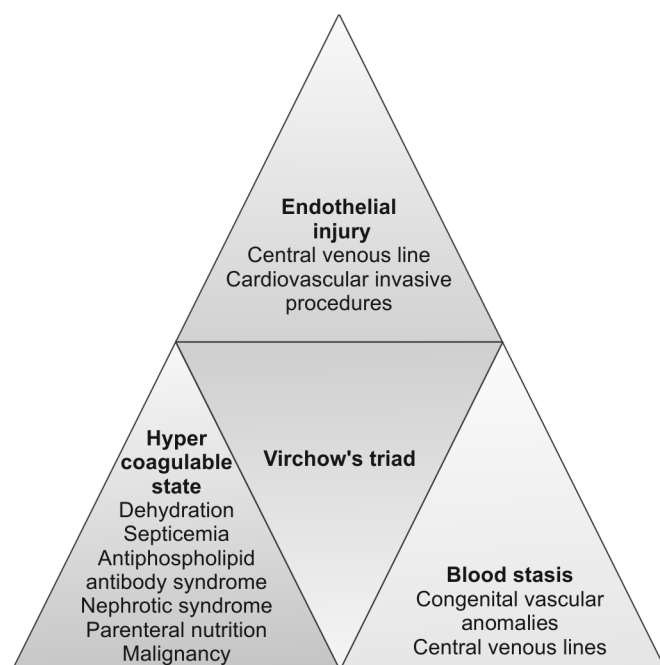


Figure 2 Image showing common acquired thrombophilic states. Acquired thrombophilic states affect one or more components of the classical Virchow's triad, which include endothelial injury, hypercoagulable state and blood stasis

Table 2 Pathophysiology underlying common acquired thrombotic states

Condition	Pathogenesis of thrombotic state
Central venous line	Stasis of blood, venous wall injury
Cyanotic congenital heart disease	Polycythemia with hyperviscosity of blood, presence of stents and prostheses
Gram-positive septicemia	Bacterial mucopolysaccharides activate platelets and serine proteases

Contd...

Contd...

Condition	Pathogenesis of thrombotic state
Gram-negative septicemia	Bacterial endotoxins cause cytokine cascade and endothelial injury
Dehydration secondary to diarrhea, ketoacidosis, poor intake, burns, high fever	Increased hematocrit and hyperviscosity of blood
Total parenteral nutrition	Dextrose and phosphate cause prothrombotic state
Nephrotic syndrome	Hyperfibrinogenemia, thrombocytosis, hemoconcentration, relative immobilization with urinary loss of antithrombin, proteins C and S
Malignancy	Thrombin production by tumor, hyperleukocytosis in leukemia leading to hyperviscosity of blood
Drugs	Oral contraceptive pills, L-Asparaginase, steroids
Inflammatory diseases (Systemic lupus erythematosus, inflammatory bowel disease, Behçet's disease)	Tissue factor release, vascular injury, antiphospholipid antibodies
Paroxysmal nocturnal hemoglobinuria	Alteration of platelet surface glycoproteins
Anemia	Iron-deficiency associated with thrombocytosis; sickle cell disease causes stasis and hyperviscosity; patients with hemolytic anemia—postsplenectomy
Miscellaneous	Injury secondary to trauma or surgery, prolonged immobilization leading to blood stasis

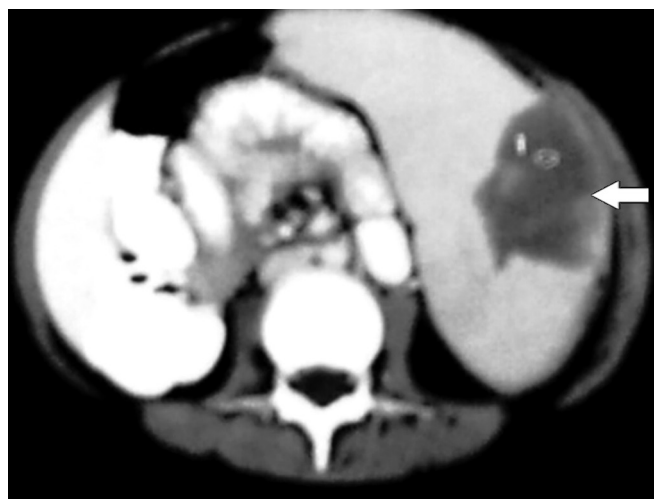


Figure 3 A 12-year-old boy with thalassemia major presented with left upper quadrant pain and tender splenomegaly. CT abdomen revealed splenic infarct (arrow). Hemoglobinopathies including thalassemia major and sickle cell disease are associated with a hypercoagulable state

CLINICAL PRESENTATION

Venous Thromboembolism

Idiopathic VTE is very rare. Majority of children have a definite underlying risk factor. An indwelling central venous line is found in 50–60% of thrombotic events. While 70% of children with VTE have a chronic medical condition such as malignancy, inflammatory

diseases or nephrotic syndrome, most of the remaining have a transient underlying insult, including infection or trauma.

Extremity Deep Vein Thrombosis (DVT)

It presents as unexplained pain and swelling of the limb. There may also be warmth, erythema of overlying skin and tenderness (**Fig. 4**). Forceful dorsiflexion of the foot can elicit pain in the calf (*Homan's sign*) and side to side squeezing of calf can elicit pain (*Moses' sign*) in DVT of lower limb. If the clot extends further proximally, bilateral limb swelling may occur. In the upper half of the body, a clot proximally extending into the superior vena cava can be associated with head and neck swelling, periorbital edema and headache.

Pulmonary Embolism

It is usually secondary to deep vein thrombosis. It manifests as sudden onset dyspnea, dry cough, hemoptysis, pleuritic chest pain and sometimes fever. Severe episodes associated with proximal or saddle emboli, lead to hypoxemia, cyanosis and collapse. A massive pulmonary embolus can obstruct the pulmonary circulation leading to right heart failure with hepatomegaly and peripheral edema.

Cerebral Venous Sinus Thrombosis (CVST)

It can have acute to subacute onset and is almost always associated with an underlying medical condition (**Table 3**). The manifestations include seizures, which are more common in newborns; and focal (cranial nerve palsies, hemisensory loss and hemiparesis) or diffuse neurological signs (headache, nausea, vomiting, blurred vision and papilledema), which are usually seen in infants and children. Any new onset neurological manifestation in the conditions listed in **Table 3** must elicit suspicion of CVST and prompt appropriate imaging.

Renal Vein Thrombosis

It may manifest as hematuria, thrombocytopenia, flank pain and enlarged kidney, which becomes palpable as a flank mass. It is most commonly seen in the newborn period, maternal diabetes being an important risk factor. In older children, it is often associated with nephrotic syndrome. One fourth of cases may show bilateral involvement. There may be uremia and oliguria, particularly with bilateral disease.



Figure 4 A 4-year-old patient with acute lymphoblastic leukemia received vincristine, steroids and L-asparaginase for induction. The patient developed sudden onset swelling of right lower limb. A Doppler ultrasound confirmed a large thrombus extending from the popliteal vein into the right common iliac vein. Malignancy, L-asparaginase and steroids contribute to a prothrombotic state

Table 3 Risk factors for cerebral venous sinus thrombosis

Adverse perinatal events	Maternal hypertension, gestational diabetes mellitus, neonatal sepsis, birth asphyxia, polycythemia, dehydration
Head and neck infections, surgery or trauma	Meningitis, otitis media, mastoiditis, sinusitis, intracranial surgery and shunts
Anemia	Iron-deficiency, sickle cell anemia, thalassemia, paroxysmal nocturnal hemoglobinuria
Autoimmune	Systemic lupus erythematosus, antiphospholipid antibody, inflammatory bowel disease
Renal disease	Nephrotic syndrome, hemolytic uremic syndrome
Cardiac disease	Cyanotic congenital heart disease, catheterization and surgery
Malignancy	Leukemia, lymphoma, L-asparaginase related, brain tumors
Miscellaneous	Dehydration, diabetic ketoacidosis, Down syndrome, homocystinuria

Other rare sites of venous thrombosis and presentation include: *hepatic vein*: right upper abdomen pain and hepatomegaly; *splenic vein*: discomfort in left upper abdomen, splenomegaly and hypersplenism; *portal vein*: abdominal pain, portal hypertension manifested as gastrointestinal bleed, ascites and splenomegaly; *mesenteric vein*: diffuse abdominal pain and ileus. Internal jugular vein thrombosis presents with neck pain and swelling, and may occur as a part of a distinct septic thrombophlebitic syndrome known as *Lemierre's syndrome*, where there is fever, trismus and painful neck movements. Lung embolism can cause dyspnea. The etiology is a parapharyngeal infection caused by *Fusobacterium necrophorum*.

Arterial Thrombosis

Peripheral arterial thrombosis is invariably related to catheterization of the artery. The involved extremity becomes cold and pale to cyanosed due to hypoperfusion. The peripheral pulses in the limb are absent or diminished (**Box 1**). Umbilical artery cannulation in newborns and cardiac catheterization in older children are important risk factors. The other common arterial thrombotic event is ischemic arterial stroke involving the cerebral vasculature, which manifests as seizures, apnea and poor feeding in newborns, and focal neurological deficit in older children.

BOX 1 Signs of arterial occlusion

- Pain
- Pallor
- Paresthesia
- Paralysis of limb
- Pulses difficult to palpate

Peripheral arterial catheters can also be thrombosed. It is important to perform *Allen test* prior to radial arterial puncture to prevent limb threatening thrombus. For this, the radial and ulnar arteries are respectively occluded with the examiner's thumb and index finger and the child's hand is raised above the head. The child is then instructed to make a fist repeatedly till the fingers turn white, following which the ulnar artery is released. If there is a delay of more than 14 sec for color to return to normal, it suggests ulnar artery insufficiency and contraindicates radial artery puncture.

INVESTIGATIONS

A complete blood count and a coagulogram with prothrombin time (PT), activated prothrombin time (aPTT) and international normalized ratio (INR) is essential as baseline prior to initiating therapy and for monitoring the anticoagulation therapy. Radiology is required for confirming diagnosis as well as defining the extent of thrombus and the degree of obstruction.

Coagulation Parameters Relevant to Thrombosis

Prothrombin time is a measure of the extrinsic pathway. Warfarin inhibits the vitamin K dependent proteins (Factors II, VII, IX, X, Proteins C and S), resulting in a prolonged PT. The therapeutic monitoring of warfarin is thus PT based. However, since PT is critically dependent on the tissue derived thromboplastins used in the assay, there is significant interlaboratory variation in reporting PT. For this reason, WHO introduced the concept of *INR*, to compare any given PT from a lab to an established international reference preparation of thromboplastin. It is calculated by the following formula:

$$\text{INR} = [\text{Patient PT} / \text{mean normal PT}]^{\text{ISI}}$$

ISI is a correction factor, which is provided by the commercial suppliers of thromboplastin preparations and is 1 for the international reference preparation. INR is thus used as the standard monitoring parameter during vitamin K antagonist therapy. aPTT measures the intrinsic pathway of coagulation and is used to monitor therapy with unfractionated heparin and other anticoagulants which inhibit thrombin. Low molecular weight heparin predominantly inhibits factor X and does not prolong aPTT. It is better monitored with anti-Xa level, when available.

D-dimer and fibrin degradation products represent ongoing thrombosis and fibrinolysis. They are increased during any thrombus formation. Their diagnostic value is limited in pediatric thrombosis, and they are not recommended as standard investigations. They have a good negative predictive value.

Radiological Investigations

Venography

It has historically been the gold standard imaging modality for VTE. However, with the availability of less invasive modalities, its role is declining. The concerns include technical difficulty, the need to inject iodinated contrast and possible risk of causing thrombus extension.

Compression Ultrasound with Doppler

It is an excellent noninvasive method for confirming and delineating a thrombus involving the distal or proximal lower extremity. The thrombosed femoral vein loses its normal compressibility with the pressure of the ultrasound transducer. Color-flow and pulsed Doppler further outline the extent of thrombus in the vein. It is also useful in renal vein, portal vein and jugular vein thrombosis. Doppler is a good modality for arterial thrombosis too, particularly in the femoral, renal and carotid arteries.

Echocardiography

It is useful in intracardiac and proximal vena caval thrombi. It is also important in diagnosis of coronary artery thrombosis and aneurysm in Kawasaki disease. It is an important aspect of work up in arterial ischemic stroke for detecting cardioembolic source and right to left shunt.

CT/MR Venography

For deeper pelvic or intra-abdominal veins, *CT venography* or if radiation exposure is a concern, *MR venography* can be used. MRI

further helps in differentiating from myositis and diagnosing May-Thurner syndrome, where the iliac vein is compressed by the right common iliac artery. CT or MRI is required to image the subclavian veins, innominate veins and the superior vena cava.

Line-o-grams with injection of radiographic contrast into central venous catheters are used for imaging line related thrombosis. *Dynamic venography* is useful in the diagnosis of Paget-Schroetter syndrome where the subclavian vein is compressed by abnormalities at the thoracic outlet, such as cervical rib. For pulmonary embolism, *helical or spiral CT* with contrast is the modality of choice with high specificity. *Ventilation-perfusion radionuclide scan* has a good negative predictive value; however, the interpretation of result needs expertise. The gold standard modality: *pulmonary angiography* is restricted to cases where intervention is being planned.

Cerebral venous sinus thrombosis is often diagnosed with the classical *empty delta sign*, a filling defect in the superior sagittal sinus on CT. A contrast CT however misses up to 40% of cases. CT venography and MRI with venography are the modalities of choice (**Figs 5A to C**). The imaging modalities are summarized in **Table 4**.

Thrombophilia Screening

Ideally every child who has experienced a thromboembolic event must undergo screening to detect an underlying thrombophilic condition. This is because it helps to identify the etiology of the event. Thrombotic events may be multifactorial and inherited thrombophilia may be uncovered by an acquired risk state for thrombosis. It enables identification of risk of recurrence and appropriate prophylactic measures. Family member counseling and screening can be offered.

Evidence is still lacking for need to screen children with catheter related thrombosis. Screening for thrombophilia must be considered in the following clinical scenarios: when young age at first episode (essentially any child); recurrent episodes of thromboembolism; unusual sites of thrombosis (cerebral veins, mesenteric veins, portal vein); warfarin induced skin necrosis (Protein C or S deficiency); neonatal purpura fulminans (Protein C or S deficiency); resistant to treatment with heparin (qualitative antithrombin defect); recurrent fetal losses and preeclampsia in pregnancy.

The investigations to be performed as part of a basic thrombophilia screening are presented in **Table 5**. During the thrombotic episode, consumption of proteins by the thrombotic process and ongoing anticoagulant therapy may interfere with the tests. Therefore, it is important to repeat following resolution of thrombosis and at least 6 months after cessation of anticoagulant drugs. Since most of the inherited thrombophilias are autosomal dominant, half the family members may be carrying the defect. Thus, screening of asymptomatic family members can be offered.

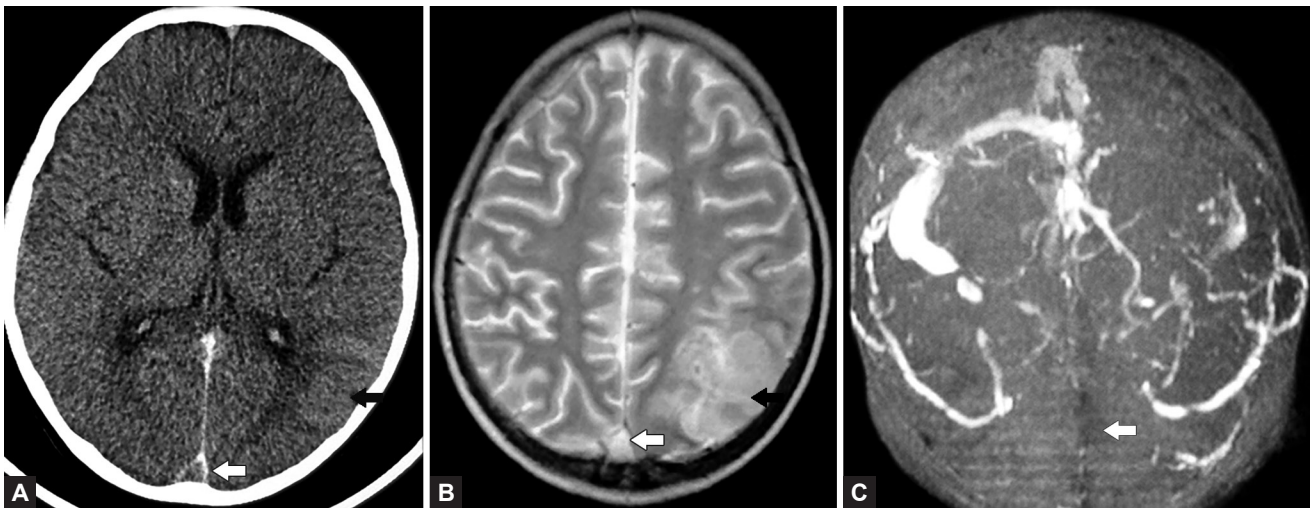
TREATMENT

The rationale of using anticoagulant therapy is to suppress the hypercoagulable state. This prevents further extension of the thrombus and embolism, and allows the intrinsic fibrinolytic system to dissolve the thrombus over time. Thrombolytic therapy is seldom used in children, unless the situation is life or limb threatening. Due to the lack of large randomized trials in children, majority of the pediatric recommendations are extrapolated from adult data.

Treatment of VTE consists of initial anticoagulation in the acute phase with unfractionated heparin (UFH) or LMWH. This is followed by an extended phase of anticoagulation with warfarin or LMWH.

Heparin

Low molecular weight heparin is increasingly being preferred over UFH due to the relative ease of administration and paucity



Figures 5A to C Neuroimaging findings of a 10-year-old patient undergoing treatment for acute lymphoblastic leukemia (ALL) who presented with altered sensorium and seizures. (A) CT head showing filling defect in the posterior aspect of the superior sagittal sinus (empty delta sign, white arrow) and hyperdense gyri in the left parieto-occipital region (black arrow); (B) T2-Flair MRI brain showing hyperintense signals in the superior sagittal sinus (white arrow) and the left parieto-occipital region (black arrow) suggestive of infarct; (C) MR venography showing gross filling defect in the superior sagittal sinus suggestive of thrombus (arrow). L-asparaginase coupled with the prothrombotic effects of steroids and the underlying malignancy predisposes to thrombosis in patients with ALL

Table 4 Radiological investigations in thrombotic conditions

Modality	Site
Compression ultrasound with Doppler	Lower limb veins, jugular veins, renal vein, portal vein; femoral artery, renal artery and carotids
CT, MRI	Deep veins of abdomen and pelvis, superior vena cava, subclavian vein, innominate vein
Line-o-gram	Central venous line related thrombi
Echocardiography	Proximal vena cava, intracardiac, cardioembolism
Helical or spiral CT, Ventilation-perfusion radionuclide scan	Pulmonary embolism
CT or MRI with venography	Cerebral venous sinus thrombosis
CT or MRI with arteriography	Arterial ischemic stroke

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging

Table 5 Investigations for thrombophilic conditions

Thrombophilic condition	Test
Protein C, protein S and antithrombin deficiency	Chromogenic or clotting assay
Factor V Leiden, prothrombin 20120A	Polymerase chain reaction
Hyperhomocysteinemia	Fasting homocysteine levels
Antiphospholipid antibody (APLA)	Phospholipid based clotting assays, ELISA for specific antibody detection

of adverse effects. Pros and cons of LMWH and UFH are given in **Table 6**. Initial heparin therapy is usually given for 5–10 days. Prolonged use of UFH in children is discouraged due to the concern of osteoporosis and is preferred in patients with increased hemorrhagic risk and renal insufficiency. During heparin therapy, platelet count should be monitored and maintained above 50,000/ μ L. The schedule for UFH is illustrated in **Figure 6**. Till target aPTT is achieved, 4 hourly aPTT monitoring is done, with dose adjustments as shown in **Table 7**.

Table 6 Comparison of low molecular weight heparin and unfractionated heparin

Parameter	Low molecular weight heparin (e.g., enoxaparin)	Unfractionated heparin (Conventional heparin)
Administration	Subcutaneous. Once or twice a day	Continuous intravenous infusion
Mechanism	Anti-Xa	Anti-Xa and IIa
Target	Anti-Xa levels 0.5–1 U/mL, 4–6 hours postinjection	APTT: 60–85 sec
Monitoring requirement	Less frequent	Intensive
Risk of heparin induced thrombocytopenia	Less	More
Reversibility with cessation	Slow	Rapid
Response to protamine	Not predictable	Predictable
Clinically labile patients and increased hemorrhagic risk	Less preferred	Preferred due to short $t_{1/2}$ and response to protamine
Patients with renal failure	Less preferred due to renal excretion	Preferred due to renal independent elimination

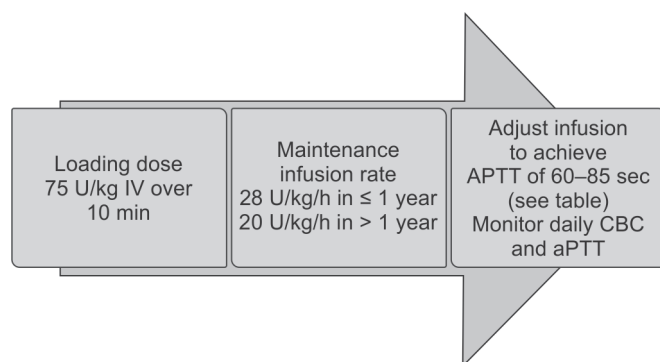


Figure 6 Protocol for administration of unfractionated heparin. Heparin infusion is initiated with a bolus dose of 75 U/kg over 10 minutes. Subsequently, a maintenance rate of 20–28 U/kg/h depending on the age is continued with 4 hourly aPTT monitoring. Infusion rates are titrated based on aPTT as described in Table 7 till the target of 60–85 sec is achieved. Subsequently daily complete blood count and aPTT are monitored as long as the infusion continues

Table 7 Titration of unfractionated heparin dose based on aPTT

APTT (seconds)	Bolus (U/kg)	Withhold for minutes	Change in dose (%)
< 50	50	0	+10
50–59	0	0	+10
86–95	0	0	–10
96–120	0	30	–10
> 120	0	60	–15

Enoxaparin is the commonly available LMWH. It is administered subcutaneously (12 hourly). The initial dose is 1.5 mg/kg/dose (< 2 months age) and 1 mg/kg/dose (> 2 months age). The other LMWH formulation available in India is dalteparin, which can be administered once a day. Ideally, an anti Xa level of 0.5–1 U/mL must be obtained at 4–6 hours after the injection, though it is not a readily available investigation.

Adverse events during heparin therapy include bleeding and heparin induced thrombocytopenia with paradoxical thrombosis. The risk of bleeding on heparin therapy ranges from 1–4%. For mild bleeding, discontinuation of UFH infusion may suffice. Protamine sulphate is indicated for immediate cessation of bleeding. The dose is dependent on time since last exposure to heparin and described in Table 8. Reversal of LMWH effect with protamine is not as predictable as with UFH. Protamine is infused in a dilution of 10 mg/mL, at a rate of not more than 5 mg/min.

Heparin induced thrombocytopenia is a rare but potentially serious complication with a frequency of 2–4% in children. It is suspected in children with a paradoxical fresh thromboembolic episode after 5–15 days of initiation of heparin, accompanied with a fall in platelet count. The pathophysiology is explained by generation of antibodies to the heparin-PF4 (Platelet factor 4) complex. The antibody-heparin-PF4 complex then binds to and activates platelets, leading to a paradoxical hypercoagulable state. Diagnosis is confirmed by detection of the antibodies by immunoassays. Treatment is with direct thrombin inhibitors, such as lepirudin, bivalirudin, argatroban and danaparoid. Warfarin and other vitamin K antagonists are contraindicated in this condition.

Vitamin K Antagonists (Warfarin)

Warfarin is the alternative drug for extended anticoagulation after the initial heparin therapy. Though other analogs such as acenocoumarol and phenprocoumon are also used in children,

Table 8 Protamine dosing in relation to time of receiving last unfractionated heparin dose

Time since last heparin dose (minutes)	Dose of protamine (mg/100 U of administered heparin dose)
< 30	1
30–60	0.5–0.75
60–120	0.375–0.5
> 120	0.25–0.375

the maximum experience and literature is on warfarin. The use of warfarin is fraught with several problems (Box 2). Warfarin initiation must overlap with the initial heparin therapy. The dose on day 1 of treatment is 0.2 mg/kg/day as a single dose (maximum 7.5 mg/day). Subsequently, dose is titrated as described in Table 9, to achieve a target INR of 2–3. Heparin is discontinued on day 6 of treatment or later if the target INR is still less than 2. The reason for the overlap is that warfarin being a vitamin K antagonist also antagonizes protein C and S, which are anticoagulant vitamin K dependent proteins. These proteins are depleted rapidly as they have a short half-life ($t_{1/2}$). This leads to a transient paradoxical prothrombotic state, until the clotting factors with longer $t_{1/2}$ get depleted as well. Infants may require higher doses (up to 0.33 mg/kg) and adolescents may require lower doses (as low as 0.09 mg/kg). Patients must be instructed to be cautious and report if there is bleeding from any site. Warfarin has drug interactions with several drugs which are used commonly, and can potentially lead to increased levels and toxicity or decreased levels and inadequate response (Box 3).

BOX 2 Difficulties with warfarin use in children

- Vitamin K dependent coagulation factors are physiologically low in newborns and increase rapidly to adult levels in infancy. This makes INR monitoring and warfarin dose titration difficult in infants
- Exclusively breastfed infants are deficient in vitamin K and thus sensitive to adverse events with warfarin. Hence require supplementation with 30–60 mL of formula feed per day
- No liquid formulation available. Tablets need to be crushed and dissolved in water for younger children with no data supporting stability in such a form. This reduces compliance as well
- No safety information in babies under 3 months of age
- Intercurrent illnesses, food items and commonly used drugs can interact with warfarin influencing its pharmacological action (Box 3).

The most concerning adverse effect is bleeding, the incidence of which is around 0.5%. Warfarin must be stopped and vitamin K administered immediately. For significant bleeding, fresh frozen plasma can be transfused; prothrombin complex concentrates and recombinant factor VIIa are other alternatives. Other adverse events reported include hair loss and reduced bone mineral density; however, are observed more in adults than in children.

Duration of Anticoagulant Therapy in VTE

The durations of anticoagulant therapy in various clinical scenarios are summarized in Table 10. The following questions are to be answered to decide the duration of therapy in any venous thromboembolic event.

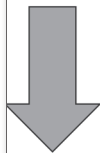
1. Is it a primary or a recurrent event?
2. Is there an underlying identifiable risk factor?
3. Is the risk factor transient (e.g., postoperative or central venous line) or long standing (e.g., Lupus)?
4. Is there an identifiable potent thrombophilic state? (e.g., homozygous deficiencies of anticoagulant proteins or factor V Leiden mutation, Antiphospholipid antibody syndrome)

Table 9 Warfarin dose titration based on INR

INR	Warfarin dose
<i>Loading dose on days 2–4</i>	
1.1–1.3	Same as day 1
1.4–3	50% of day 1 dose
3.1–3.5	25% of day 1 dose
> 3.5	Hold; once INR < 3.5, restart at 50% of previous dose
<i>Maintenance dose from day 5 onwards</i>	
1.1–1.4	Increase previous dose by 20%
1.5–1.9	Increase previous dose by 10%
2–3	No change
3.1–3.5	Decrease previous dose by 10%
> 3.5	Hold; once INR < 3.5, restart at 80% of previous dose

BOX 3 Warfarin drug interactions**Increase in warfarin's effect**

Chloramphenicol, sulfonamides, metronidazole
Cimetidine, omeprazole
Fluconazole
Nonsteroidal anti-inflammatory drugs
Selective serotonin reuptake inhibitors
Zafirlukast
Mega doses of vitamin A and E
Quinidine

**Decrease in warfarin's effect**

Vitamin C
Barbiturates, carbamazepine
Cloxacillin, rifampicin
Griseofulvin
Cholestyramine
Sucralfate
Spironolactone
Oral contraceptive pill
Vitamin K rich foods: Green leafy vegetables, liver, meat.

Thrombolysis in Pediatric Thrombosis

Conventional anticoagulant therapy is the cornerstone of managing pediatric thromboembolic event. However, thrombolytic therapy has role in selected circumstances which are life or limb threatening. The indications and contraindications of thrombolysis in children are described in **Boxes 4 and 5**.

There is no consensus on the choice or administration route of thrombolytic agent. The commonly used agent is tissue plasminogen activator (tPA), followed by urokinase, which is a cheaper option. Use of Streptokinase in children is discouraged due to the risk of severe hypersensitivity reactions and production of long lasting neutralizing antibodies. The conventional method of administration of tPA is as an intravenous infusion (0.1–0.5 mg/kg/ hours for 6 hours). Continuous infusions of lower doses over 24–96 hours and catheter directed thrombolytic administration has also been described. Urokinase is infused at a loading dose of 4400 U/kg over 5 minutes, followed by the slow infusion of same dose over 12–72 hours.

The biggest concern with thrombolytic therapy is hemorrhage. The incidence ranges from 0–40%. It may be life threatening: intracranial bleed, retroperitoneal bleed, bleed requiring surgical intervention and bleed resulting in acute fall of hemoglobin by greater than or equal to 2 g/dL. As such, careful monitoring

Table 10 Duration of anticoagulation in venous thromboembolism (VTE)

Situation	Underlying risk factor	Total duration of therapy
First episode of venous thromboembolism (VTE)	CVD	6 weeks–3 months if CVD removed* As long as in situ if retained
	Transient	3–6 months
	Chronic	12 months–lifelong
Recurrent VTE	Idiopathic	6–12 months
	Transient	6–12 months
	Chronic	Lifelong
Renal vein thrombosis	Idiopathic	12 months to lifelong
		6 weeks to 3 months
		3–6 months
Cerebral venous sinus thrombosis#		6 months
Massive thrombus with organ dysfunction		6 months
Pulmonary embolism		6 months

*CVD: Central venous device, if its patency fails to be established or it is no longer needed it should be removed *after* 3–5 days of anticoagulation to prevent embolism

#Anticoagulation to be given even if there is minimal associated hemorrhage. In case of significant associated hemorrhage reassess after 5–7 days and start anticoagulation if the thrombus shows evidence of extension

BOX 4 Indications for thrombolytic therapy**Life threatening (Strong indications)**

1. Shunt obstruction in complex cyanotic congenital heart disease
2. Massive pulmonary embolism with hemodynamic instability
3. Large atrial thrombus
4. Obstructive superior vena cava syndrome
5. Cerebral venous sinus thrombosis with worsening neurological status
6. Bilateral renal vein thrombosis

Limb threatening

1. Acute iliofemoral thrombosis
2. Inferior vena cava thrombosis
3. May-Thurner syndrome
4. Paget-Schroetter syndrome.

BOX 5 Contraindications to thrombolysis

- Ongoing bleeding
- Seizures in last 2 days
- Invasive procedure in last 2 weeks
- *Major surgery:* CNS surgery, trauma or intracranial bleed in last 2 months
- Systemic sepsis
- *CNS pathology likely to bleed:* Aneurysm, vascular malformation or tumor
- Inability to achieve a platelet count of > 75,000/μL or fibrinogen > 100 mg/dL
- Serum creatinine > 2 mg/dL
- Uncontrolled hypertension.

is required during administration. Adequate platelet count and fibrinogen levels should be ensured prior to initiation and monitored 6–12 hourly during administration. A repeat imaging to assess response can be repeated at 24 hours. D-dimer assay can be done to document evidence of thrombolysis. Conventional anticoagulation must be started with the thrombolysis and continued for an appropriate duration as per the clinical condition.

Other Anticoagulant Drugs

Other anticoagulant inhibitors include direct thrombin or factor Xa inhibitors (**Table 11**). The predominant indication is heparin induced thrombocytopenia, where heparin has to be stopped and warfarin is contraindicated. This is important in patients who are critically dependent on anticoagulation, such as patients on extracorporeal membrane oxygenation or cardiac assist devices. They all carry risk of bleeding.

Other Modalities

Surgical thrombectomy may be used prior to anticoagulation in life threatening massive venous thrombosis, pulmonary embolism and shunt thrombosis in patients with complex congenital heart disease. Inferior vena cava filter is a device inserted through femoral or jugular approach in children more than 10 kg, who have a lower limb DVT and in whom anticoagulation is contraindicated. A temporary filter is preferred over a permanent one, as it can be retrieved following resolution of the thrombus or when anticoagulation can be initiated.

Outcomes after Venous Thromboembolism (VTE)

Thromboembolic events in children are complicated by immediate or short-term complications, and chronic or long-term sequelae. Mortality rates of 1–4% are associated with large venous thrombosis. Up to two times increased in-hospital mortality is observed in children with VTE. This emphasizes the need for prompt initiation of anticoagulant therapy.

The short-term complications are: (1) Pulmonary embolism (occurs in 15–20% of venous thrombosis), (2) Superior vena cava syndrome in DVT of upper venous system, (3) Acute renal insufficiency in renal vein thrombosis, particularly if bilateral and in neonates, (4) Intracardiac thrombus or proximal pulmonary embolus leading to critical hemodynamic instability, (5) Catheter related thrombosis causing catheter malfunction and necessitating removal, (6) Occlusive DVT of lower limbs may lead to venous gangrene, (7) Complications of anticoagulant therapy, mainly bleeding, and (8) Post-thrombotic hemorrhage in brain.

The long-term sequelae are: (1) Recurrent venous thromboembolism: in up to 6–11% of primary VTE (less compared to adults); (2) Post thrombotic syndrome: A syndrome of chronic venous obstruction and valvular insufficiency following limb DVT. It is characterized by limb edema, pain, limitation of activities, visible tortuous and dilated collateral superficial veins, stasis dermatitis and ulcers. It occurs in nearly one third of children with extremity DVT; (3) Chronic hypertension and kidney injury in

Table 11 Other available anticoagulants

Drug	Mechanism of action	Administration	Monitoring parameter
Lepirudin	Antithrombin	Continuous infusion	aPTT, ACT
Bivalirudin	Antithrombin	Continuous infusion	aPTT, ACT
Argatroban	Antithrombin	Continuous infusion	aPTT
Danaparoid	Anti-Xa	Continuous infusion	Anti-Xa activity
Fondaparinux/ Idraparinux	Anti-Xa	Subcutaneous	None
Dabigatran	Antithrombin	Oral	None
Rivaroxaban	Anti-Xa	Oral	None

Abbreviation: ACT, activated coagulation time

renal vein thrombosis; (4) Portal hypertension and variceal bleed in portal vein thrombosis; (5) Neurological sequelae in cerebral venous sinus thrombosis.

Adverse prognostic indicators in thromboembolic events are: (1) Inappropriate, inadequate or delayed anticoagulation; (2) Failure of resolution of the thrombus completely with therapy; (3) Underlying inherited thrombophilia or antiphospholipid antibody; (4) Elevated factor VIII activity and D-dimer concentration at diagnosis, as well as after 3–6 months of anticoagulation.

Treatment of Arterial Thrombosis

The treatment for arterial thrombosis includes antiplatelet drugs, including aspirin and clopidogrel, in addition to heparin and warfarin. Aspirin is administered at 1–5 mg/kg/day for antiplatelet action. Acute femoral arterial thrombosis, if untreated, can progress to unsalvageable limb gangrene. Treatment starts with UFH or LMWH (similar to that described for treatment of VTE) for 5–7 days. If there is no response and/or the thrombus extends further proximally, thrombolysis must be considered. If thrombolysis is contraindicated, surgical intervention must be sought for thrombectomy. If a peripheral artery thrombosis is secondary to an arterial catheter, the catheter must be removed immediately.

In Kawasaki disease, coronary arteries are selectively affected with complications of aneurismal dilation and thrombosis. Aspirin is started at an anti-inflammatory dose of 80–100 mg/kg/day for the initial 2 weeks and continued at antiplatelet doses for 6–8 weeks. Warfarin must be added in case of moderate or giant aneurysms. Coronary artery thrombosis is a life threatening event needing thrombolysis or surgical thrombectomy. The anticoagulation/antiplatelet therapy for arterial ischemic stroke is outlined in **Table 12**.

Table 12 Antiplatelet and anticoagulant drugs in arterial ischemic stroke (AIS)

Age	Situation	Initial therapy	Extended therapy
Newborn	First episode, no cardioembolic source	Supportive care alone	
	Cardioembolic source	UFH/LMWH	LMWH*
	Recurrent AIS	Aspirin/LMWH	Aspirin/LMWH*
Older children	First episode, no embolism or dissection	UFH/LMWH/ aspirin till embolism or dissection ruled out	Aspirin for 2 years
	Recurrent AIS or transient ischemic attacks on aspirin	—	Change to clopidogrel/LMWH/ warfarin*
	Cardioembolic source	LMWH	LMWH/warfarin for 3 months#. Repair right to left shunt
	Dissection	LMWH	LMWH/warfarin for 6 weeks#
	Nonmoyamoya vasculopathy	LMWH	LMWH/warfarin for 3 months#
	Moyamoya vasculopathy	Aspirin	Refer to center with revascularization expertise

Abbreviations: UFH, unfractionated heparin; LMWH, low molecular weight heparin

*Duration of therapy based on clinical and radiological monitoring and response

#The duration mentioned is the minimum needed, it may be prolonged in case of clinical recurrence or persistence of thrombus

IN A NUTSHELL

1. Pathologic tendency to develop excessive and unwanted thrombosis is called thrombophilia.
2. Inherited thrombophilia is due to mutations in genes involved in anticoagulant protein production. Conditions include deficiency of protein C, protein S, antithrombin and mutations involving factor V Leiden, prothrombin and *MTHFR*.
3. Acquired thrombophilia is secondary to the classical Virchow's triad of thrombosis: stasis, hypercoagulable state and endothelial injury. Common etiology: nephrotic syndrome, central venous line, systemic lupus erythematosus and malignancies.
4. Clinical features depend on the site of thrombosis. Few commonly encountered sites include deep vein thrombosis (DVT) in limbs, pulmonary embolism and cerebral venous sinus thrombosis (CVST).
5. Doppler ultrasound is the best modality to detect DVT in the lower extremity. Spiral/helical CT and ventilation-perfusion scans are used for diagnosing pulmonary embolism. MRI with venography is the modality of choice for CVST.
6. A screening for common inherited thrombophilic states is desirable following all noncatheter related thrombosis in children. The investigations are performed following resolution of thrombosis and discontinuation of anticoagulant drugs.
7. Treatment of venous thromboembolism in children involves initial anticoagulation using UFH or low molecular weight heparin (LMWH) followed by an extended phase of anticoagulation with LMWH or warfarin.
8. Low molecular weight heparin is typically preferred over UFH. Enoxaparin the commonly available LMWH. It is administered subcutaneously, 12 hourly, at 1.5 mg/kg/dose in less than 2 months age and 1 mg/kg/dose in older patients.
9. Warfarin is started after an initial overlap with heparin therapy at a dose of 0.2 mg/kg/day and subsequently titrated to achieve an INR of 2–3.
10. The duration of anticoagulation varies, depending on site, underlying risk factors and whether the thromboembolic event is a primary or recurrent event.

MORE ON THIS TOPIC

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Chapter 38.23

Disseminated Intravascular Coagulation

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Disseminated intravascular coagulation (DIC) is a systemic disorder characterized by intravascular activation of the coagulation system leading to intravascular thrombi, compromising an adequate blood supply to the organs, and to bleeding as a consequence of exhaustion of the platelets and coagulation factors. Hence, a patient with DIC can present with features of intravascular thrombosis and hemorrhagic manifestations at the same time. DIC never occurs in isolation and is always secondary to a pre-existing primary pathology.

EPIDEMIOLOGY

The frequency of DIC in hospitalized patients is approximately 1.72%. Sepsis is the most important etiological factor in all age groups. DIC may occur in 30–50% of patients with gram-negative sepsis and may be a predominant feature of severe infection. DIC occurs at all ages with no particular sex predisposition.

ETIOLOGY

Disseminated intravascular coagulation is not itself a specific illness. It is a clinicopathological syndrome which complicates a number of illnesses. All these culprit illnesses have the ability to induce systemic activation of coagulation system either by activating cytokines or by causing the release of, or exposure to procoagulant factors (**Box 1**).

PATHOPHYSIOLOGY

Disseminated intravascular coagulation is the result of several simultaneously occurring mechanisms. The systemic formation of fibrin is a result of tissue factor-mediated thrombin generation and the simultaneous suppression of physiologic anticoagulation mechanisms such as the antithrombin system and the protein C system. In addition, there is delayed removal of fibrin as a consequence of impaired fibrinolysis. In some forms of DIC, fibrinolytic activity may be increased and may further contribute to bleeding. The initial phase of DIC consists of formation of microvascular thrombi in kidneys and lungs with subsequent end organ dysfunction. In the second phase, there is wide-spread activation of fibrinolysis and consumption of coagulation factors and platelets. The resultant severe consumption coagulopathy leads to uncontrolled bleeding from wounds and spontaneous hemorrhage into gut, brain and other tissues (**Fig. 1**).

Several mechanisms which play role in the pathogenesis include (1) Tissue factor (TF) mediated thrombin generation (2) Suppression of physiologic anticoagulant mechanisms (3) Impaired fibrin removal due to depressed fibrinolysis.

Tissue factor can trigger the extrinsic pathway of coagulation. Increased tissue factor production is considered the most important for the onset of DIC. Its activity in peripheral blood is markedly increased following tissue injury and activation of monocytes. The increased tissue factor activity results in the transformation of prothrombin to form fibrin thrombus.

Disseminated Intravascular Coagulation in Sepsis

Septicemia is the most common clinical condition associated with DIC. Although virtually all microorganisms can cause

BOX 1 Conditions associated with disseminated intravascular coagulation

1. *Neonatal causes*
 - Perinatal asphyxia, respiratory distress syndrome, meconium aspiration, amniotic fluid aspiration, necrotizing enterocolitis, metabolic disorders, congenital intrauterine infections, bacterial and fungal infections, congenital homozygous protein C/S deficiency
2. *Infections*
 - Bacterial (e.g., gram-negative, gram-positive infection, rickettsial infection)
 - Viral [e.g., HIV, cytomegalovirus (CMV), varicella-zoster, hepatitis, dengue, influenza]
 - Fungal (e.g., histoplasma)
 - Parasite (e.g., malaria)
3. *Trauma*
 - Neurotrauma
 - Crush injury
 - Severe burn injury
 - Fat embolism
4. *Organ destruction*
 - Pancreatitis
 - Severe hepatic failure
5. *Malignancy*
 - Solid tumors
 - Lymphoproliferative/myeloproliferative malignancies
6. *Immunologic*
 - Acute hemolytic transfusion reaction
 - Transplant rejection
7. *Vascular abnormalities*
 - Kasabach-Merritt syndrome
 - Large vascular aneurysm
8. *Severe toxic reactions*
 - Snake bite
 - Drugs
9. *Heat stroke and hyperthermia*
10. *Hemorrhagic skin necrosis*
 - Purpura fulminans.

DIC, bacterial infection is most frequently associated with the development of DIC. Clinically overt DIC may occur in 30–50% of patients with gram-negative sepsis. DIC in sepsis is mediated by several proinflammatory cytokines. The principal mediator of activation of coagulation is interleukin-6, and it is the principal mediator of the dysregulation of the physiologic anticoagulation pathways and the fibrinolytic defect.

Mechanisms Involved in the Pathogenesis of DIC in Sepsis*Increased Thrombin Generation*

It is predominantly mediated by tissue factor/factor VIIa pathway and reduced antithrombin levels which result from increased consumption, enzyme degradation by elastase released from activated neutrophils, impaired synthesis due to liver failure and increased capillary leakage.

Impaired Function of Physiological Anticoagulant Pathway

Reduced antithrombin levels as previously described along with significant depression of protein C system caused by increased consumption, impaired hepatic synthesis, vascular leakage and downregulation of thrombomodulin expression by pro-inflammatory cytokines like tumor necrosis factor (TNF)- α and interleukin (IL)-1 β .

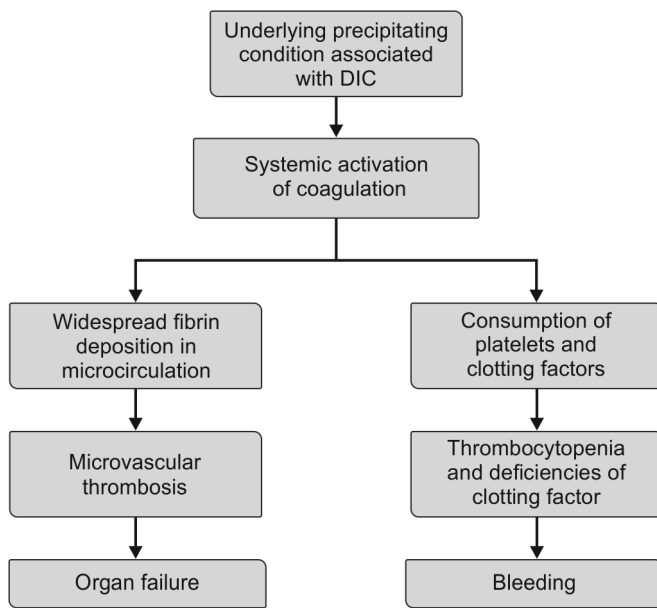


Figure 1 Pathophysiology of disseminated intravascular coagulation (DIC)

Impaired Fibrinolysis

Initial hyperfibrinolytic response due to release of plasminogen activator from endothelial cell is followed by rapid suppression of fibrinolytic activity due to increase in plasma levels of plasminogen activator inhibitor type I (PAI-I) levels. Functional mutation in PAI-I gene is associated with worst clinical outcome in patients with meningococcal sepsis.

Activation of Inflammatory Pathway

It is mediated by activated coagulation proteins and depression of protein C system which has an anti-inflammatory effect through inhibition of endotoxin-induced production of TNF- α , IL-1 β , IL-6 and IL-8.

Polytrauma, because of physical force, burns or heat stroke may result in DIC due to a combination of mechanisms including hemolysis, endothelial activation, release of tissue material into the circulation (fat, phospholipids) and acidosis because of hypoperfusion.

TYPES OF DISSEMINATED INTRAVASCULAR COAGULATION

Disseminated intravascular coagulation can present as acute (decompensated) or chronic (compensated) form.

Acute disseminated intravascular coagulation Acute form presents when there is exposure of blood, over a brief period, to procoagulants (e.g., tissue factor or tissue thromboplastin), which generate intravascular coagulation. As a result of this, there may be profound bleeding due to consumption coagulopathy or diffuse microvascular thrombosis leading to end-organ damage or a combination of both.

Chronic disseminated intravascular coagulation In chronic DIC, the exposure to the triggering factor is slow. The compensatory mechanisms in the liver and bone marrow replenish the factors by increased production. There may be little obvious clinical or laboratory indication of presence of DIC. Chronic DIC is more frequently seen in malignancies, large aortic aneurysms and vasculitis.

CLINICAL MANIFESTATIONS

The clinical presentation and consequences of DIC depend on the etiology and the rapidity of the initiating event. Acute events lead to intravascular coagulation with depletion of platelets and procoagulant factors, production of fibrin degradation products and bleeding. Acute DIC may be fatal unless the condition is diagnosed early and appropriate treatment initiated.

In addition to the symptoms related to the underlying disease process, there is typically a history of blood loss through bleeding in the areas such as the gingivae and the gastrointestinal system. Acutely presenting DIC often manifests as petechiae on the soft palate, trunk and extremities because of thrombocytopenia and ecchymosis at venipuncture sites and traumatized areas. There may be blood loss from intravenous lines and catheters. In postoperative DIC, bleeding can occur in the vicinity of surgical sites, drains, tracheostomies as well as within serous cavities. Bleeding from at least three unrelated sites is particularly suggestive of DIC. Patients with pulmonary involvement can present with dyspnea, hemoptysis and cough. Comorbid liver disease as well as rapid hemolytic bilirubin production may lead to jaundice. Neurological changes (e.g., coma, altered sensorium and paresthesia) are also possible. One should look for symptoms and signs of thrombosis in large vessels (e.g., deep vein thrombosis) and microvascular thrombosis (e.g., in renal failure). As many as 25% patients with DIC present with renal failure. In patients with chronic DIC, the signs of venous thromboembolism may be present because of thrombosis from excessive thrombin formation.

APPROACH TO DIAGNOSIS

No single laboratory assay is pathognomonic of DIC. Hence, it is very important to assess the entire clinical picture, taking into account the clinical condition of the patient, the diagnosis, and all available laboratory results. DIC is an extremely dynamic situation and each laboratory test describes the state at that particular point of time. A combination of tests when repeated in a patient with a clinical condition known to be associated with DIC can be used to diagnose the disorder with reasonable certainty in most cases. However, in clinical practice DIC can be diagnosed on the basis of the presence of an underlying condition known to cause DIC, low platelet count or a rapid fall in the platelet count, prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT), presence of fibrin degradation products (FDPs) in plasma, low plasma levels of plasma inhibitors of coagulation like antithrombin III and protein C.

A combination of prolonged PT, hypofibrinogenemia and thrombocytopenia in an appropriate clinical setting is sufficient to suspect the diagnosis of DIC in most instances. To confirm the diagnosis of DIC, tests that indicate increased fibrinogen turnover (i.e., elevated fibrin degradation products—FDPs or D-dimer assay) may be necessary. The D-dimer assay has been shown to be highly sensitive and specific for proteolytic degradation of polymerized fibrin.

INVESTIGATIONS

Platelet Count

A low platelet count or a rapid fall at subsequent measurements is a sensitive though not a specific indicator of DIC. A low platelet count strongly correlates with thrombin generation as thrombin induced platelet aggregation is responsible for platelet consumption. A continuous fall even within normal range may indicate the active generation of thrombin, whereas, a stable platelet count suggests cessation of thrombin formation. It is important to note that many conditions that are associated with DIC may also cause a low platelet count in the absence of DIC.

Peripheral Blood Smear

The peripheral blood smear may demonstrate schistocytes, though they rarely exceed 10% of red blood cells. Presentation of schistocytes is neither sensitive nor specific for DIC. It may help in making a diagnosis of chronic DIC when schistocytes are seen with normal coagulation values and increased D-dimer value.

Prothrombin Time, Activated Partial Thromboplastin Time and Coagulation Factors

Prothrombin time and aPTT are generally prolonged. However, normal values or even shortening of either PT or aPTT or both do not exclude the diagnosis of DIC. This prolongation of PT and aPTT is mainly due to consumption of coagulation factors, impaired synthesis, loss of coagulation proteins and vitamin K deficiency. The consumption and depletion of various coagulation factors may be further confirmed by the measurement of coagulation factors such as V, VII and VIII. It is important to note that serial measurements of coagulation tests are more helpful than a single laboratory result in confirming the diagnosis of DIC. Another point to note is that the PT, not the international normalized ratio (INR), should be used in DIC monitoring as INR is recommended only for monitoring anticoagulant therapy.

Tests for Fibrin and Fibrin Degradation Products and D-Dimer

Fibrin generation is the key component of DIC. Hence, demonstration of elevated levels of soluble fibrin, to establish the diagnosis of DIC, seems logical. Most of the studies have shown that soluble fibrin measurement is highly sensitive (90–100%) but has very low specificity. Moreover, there is a major problem in reliable quantification of soluble fibrin and the test is also not routinely available.

An important component of DIC is fibrinolysis. Therefore, there will be evidence of fibrin breakdown, such as elevated levels of FDPs and D-dimer. The specificity of high levels of FDPs and D-dimer is limited as many other conditions such as thromboembolism, trauma, recent surgery and inflammation may be associated with raised levels of FDPs and D-dimer. Impairment of kidney and liver functions may also influence their levels. Testing for FDPs and D-dimer may be useful for differentiating DIC from other conditions which are associated with a low platelet count and prolonged clotting time values. Exact cut off levels of FDPs and D-dimer to grade DIC have not been established.

Fibrinogen

Low fibrinogen levels are only present in about one third of the patients of DIC as a result of consumption. Fibrinogen is an acute phase reactant, it may be high in conditions of inflammation and hence, the levels may be falsely normal. Sequential measurements of fibrinogen levels may point towards consumption coagulopathy occurring in DIC.

Anticoagulants

Proteins C and antithrombin III are the two natural anticoagulants that are frequently decreased in DIC. Their single measurements are neither sensitive nor specific for DIC. Low levels of protein C may indicate severity of DIC. They may be useful as prognostic indicators.

Specialized Tests

Activation markers which are released upon the conversion of the coagulation factor zymogen to an acute protease such as prothrombin activation fragment F1 + 2 (F1+2) are markedly increased in DIC but their specificity is not good.

Serum levels of thrombomodulin are elevated in DIC, which correlate well with severity of DIC and also can serve as a marker for early detection and monitoring of DIC. Thromboelastography (TEG) technique provides information about the coagulability of blood at a particular time. Its diagnostic use in DIC is still being evaluated. An atypical light transmittance profile of aPTT resulting in a biphasic waveform abnormality has been shown to be a good indication of DIC and this often precedes any abnormality in the more conventional parameters used for diagnosing DIC.

Most of the tests show high sensitivity but low specificity. DIC is a rapidly changing process and these tests give an idea of patient's condition at that particular point of time. It is important to remember that repeated tests may, therefore be required to make a more clinical certain diagnosis. Tests like PT, aPTT, platelet count, FDPs and D-dimer are commonly available and are sufficient to make or exclude clinical diagnosis of DIC.

In 2001 the International Society on Thrombosis and Hemostasis (ISTH) proposed a scoring system for the diagnosis of DIC, whose prerequisite is the presence of an underlying disorder known to be associated with DIC. A diagnosis of overt DIC is made with a score more than or equal to 5. This scoring system has sensitivity of 91%, whereas, the specificity is 97%. A positive correlation between an increasing DIC score (**Box 2**) and mortality has been shown by several studies. A major disadvantage of the diagnostic score is that it is a static assessment, which may not capture the dynamically changing scenario of the coagulopathy.

BOX 2 Scoring system for overt disseminated intravascular coagulation

- **Risk assessment:** Does the patient have an underlying disorder known to be associated with overt DIC?
 - *If no:* Do not use this algorithm
 - *If yes:* Proceed, order global coagulation tests (PT, platelet count, fibrinogen, fibrin related marker) and score the test results
 - Platelet count ($> 100 \times 10^9/L = 0$, $< 100 \times 10^9/L = 1$, $< 50 \times 10^9/L = 2$)
 - Elevated fibrin marker (e.g., D-dimer, fibrin degradation products) (no increase = 0, moderate increase = 2, strong increase = 3)
 - Prolonged PT ($< 3 \text{ sec} = 0$, $> 3 \text{ but } < 6 \text{ sec} = 1$, $> 6 \text{ sec} = 2$)
 - Fibrinogen level ($> 1 \text{ g/L} = 0$, $< 1 \text{ g/L} = 1$)
- **Calculate score**
 - > 5 compatible with overt DIC: Repeat score daily
 - < 5 suggestive for nonovert DIC: Repeat next 1–2 days.

DIFFERENTIAL DIAGNOSIS

Conditions that may produce clinical manifestations and laboratory abnormalities similar to those in DIC include liver disease, hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, primary fibrinogenolysis and massive transfusion.

Patients with liver disease may present with coagulation abnormalities and clinical manifestations similar to DIC patients. However, these conditions may be differentiated by measurement of clotting factor activity. In liver disease, factor VII and IX are typically low and factor VIII may be normal or increased. Whereas, in DIC factor VII is mildly decreased and factor VIII is decreased as well. Another useful test is D-dimer assay, which is abnormal in DIC but normal in liver disease.

Hemolytic uremic syndrome is commonly associated with anemia and renal insufficiency. High levels of FDPs may be seen but coagulation abnormalities are not commonly present. Patients with thrombotic thrombocytopenic purpura have anemia, renal abnormalities and neurological changes in addition to thrombocytopenia.

Cases with primary fibrinolysis have hypofibrinogenemia, increased levels of FDPs, abnormal PT, aPTT and thrombin time and deficiency of factor V and VIII. However, platelet count is generally normal and D-dimer level is normal or minimally elevated. Massive transfusion may present with coagulation abnormalities and decreased fibrinogen and clotting factor levels but FDPs and D-dimer are normal.

MANAGEMENT

The cornerstone of the management of DIC is the specific and vigorous treatment of the underlying condition. In most of the cases, DIC will spontaneously resolve when the underlying disorder is appropriately managed. Examples include the administration of antibiotics, antsnake venom or surgical drainage in patients with DIC. Additional supportive therapy in the form of plasma and blood transfusions, platelet substitution therapy, anticoagulants, and administration of physiologic coagulation inhibitors may be required.

Blood Component Therapy

Blood component therapy should be based on whether the patient is bleeding or requiring an invasive procedure, or at risk of bleeding. It should not be instituted on the basis of laboratory results alone.

Replacement of missing blood components should be instituted as necessary. Packed erythrocytes are required if the patient is bleeding profusely. Platelet transfusions should be considered in patients with active bleeding or at high risk of bleeding and a platelet count of less than $50 \times 10^9/L$. In non-bleeding patients with DIC, prophylactic platelet transfusion is not given unless it is felt that there is high risk of bleeding. Replacement therapy for thrombocytopenia is aimed at raising the platelet count to $20\text{--}30 \times 10^9/L$ and to $50 \times 10^9/L$ in patients who need an invasive procedure.

In patients with active bleeding or who require an invasive procedure, and have prolonged PT and aPTT, administration of fresh frozen plasma (FFP) in the dose of 15 mL/kg is recommended. If transfusion of FFP is not possible such as in patients with fluid overload and bleeding, administration of factor concentrates like prothrombin complex concentrate may be useful. These concentrates may partially correct the defect as they contain only selected coagulation factors, whereas, patients with DIC usually have a deficiency of all coagulation factors. Severe hypofibrinogenemia ($< 1 \text{ g/L}$) that persists despite FFP replacement may be corrected by cryoprecipitate or fibrinogen concentrate.

The response to blood component therapy should be monitored both clinically and by repeated assessment of platelet counts and coagulation tests following administration. The efficacy and safety of recombinant factor VIIa in DIC patients with massive bleeding are unknown and this should be used with caution.

Anticoagulants

Heparin has been shown to be beneficial in small and uncontrolled studies of patients with DIC, but not in controlled clinical trials. The administration of heparin is not recommended in DIC patients with bleeding because of the increased risk of bleeding. However, therapeutic doses of heparin should be considered in cases with DIC in which thrombosis is the primary feature. When thrombotic event is associated with DIC (such as arterial, venous or purpura fulminans), heparin should be used in the dose of 10 IU/kg/h. Patients with an increased risk of bleeding may be given unfractionated heparin due to its short half-life. Low

molecular weight heparin and mechanical methods can also be used. The target aPTT in such cases should be around 1.5–2.5 times the normal or 59–85 sec. Monitoring the aPTT in these cases may be complicated and clinical observation for signs of bleeding is important. In critically ill and nonbleeding patients with DIC, prophylaxis for venous thromboembolism with prophylactic doses of heparin or low molecular weight heparin is recommended.

Conceptually, the use of anticoagulant agents effective against tissue factor activity seems to be most logical. Although, phase II trials of recombinant tissue factor pathway inhibitor (TFPI) in patients with sepsis showed encouraging results, a phase III trial did not show an overall survival benefit. Recent trials of recombinant human thrombomodulin suggest that this compound may reduce mortality and may reduce the severity of organ failure significantly.

Concentrate of Coagulation Inhibitors

The use of anticoagulant factors such as antithrombin and activated protein C to restore the dysfunctional anticoagulant pathway in DIC is not recommended in pediatric patients. Antithrombin concentrate has been available since 1980s and most trials with this compound show some benefit in terms of improvement of laboratory parameters but no clinical trial has been able to demonstrate improved mortality. Based on the logic that there is depression of the protein C pathway in DIC, it has been suggested that supplementation of activated protein C might potentially be of benefit. Some studies have shown the ability of activated protein C to normalize coagulation activation during severe sepsis, but it has also been reported to increase the risk of major bleeding. Unlike in adults, use of activated protein C is not recommended in children with DIC. In fact, because of an increased risk of bleeding and lack of efficacy, a randomized clinical trial of activated protein C in children with severe sepsis was terminated early.

Antifibrinolytic Agents

The use of antifibrinolytic agents such as tranexamic acid in patients with DIC is generally not recommended because DIC has hypofibrinolysis and antifibrinolytic agent might worsen the condition by prothrombotic effect. The only exception may be made in patients with primary or secondary hyperfibrinolysis (e.g., coagulopathy associated with promyelocytic leukemia or in some cases of DIC secondary to other malignancies), where antifibrinolytic treatment has been shown to control coagulopathy. The use of procoagulant factor concentrate like prothrombin complex or recombinant factor VIIa is not recommended for the treatment of DIC patients with coagulopathy as they may worsen the condition.

PROGNOSIS

In general, presence of DIC worsens prognosis in all disorders. Development of complications such as shock, hemorrhage, thrombosis and renal failure are associated with increased mortality. DIC is an independent predictor of mortality in patients with sepsis and trauma. It is difficult to state the mortality and morbidity of DIC as both DIC and its underlying condition contribute to these. Overall mortality of severe acute DIC ranges from 50–70%. However, if the underlying condition is self-limiting or can be controlled, DIC will disappear and the coagulation status will be normalized. With the early recognition of systemic abnormalities and the introduction of new therapies, the prognosis for many patients with DIC has improved over the last several years.

IN A NUTSHELL

1. DIC is an acquired thrombohemorrhagic syndrome in which a patient can present with thrombotic and bleeding problems at the same time.
2. DIC never occurs in isolation and is always secondary to a pre-existing primary pathology.
3. Sepsis is the most common etiological agent of DIC. Administration of appropriate antibiotics is of paramount importance.
4. Thrombin generation, suppression of physiological anticoagulants (such as antithrombin III, protein C and tissue factor pathway inhibitor) and decreased fibrinolysis play key role in pathogenesis of DIC.
5. There is no single laboratory test that allows a definite diagnosis of DIC.
6. In a clinical situation, a combination of prolonged PT, aPTT, thrombocytopenia and elevated fibrin degradation products along with a condition known to cause DIC is sufficient to make a diagnosis of DIC.
7. Early recognition and effective control of the underlying disease are paramount to ensure successful management of acute DIC.
8. The treatment of choice for DIC remains vigorously treating the underlying triggering condition along with supporting the hemostatic components.
9. Clinical condition of the patient (e.g., bleeding) should guide replacement therapy rather than laboratory values.
10. Presence of DIC worsens prognosis in all disorders.

MORE ON THIS TOPIC

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Chapter 38.24

Blood Component Therapy

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Blood component transfusion is one of the mainstays of treatment across pediatric patients who are one of the intensively transfused patients and also one of the most vulnerable groups of transfusion recipients. Blood transfusion needs in pediatric group especially for infants are different due to small volume of patients and immature organs which necessitate special approaches to component therapy. This chapter deals with a number of specialized pediatric transfusion situations including the technical considerations and biomedical devices required for the transfusions. The goal is to provide a resource for a safe and most effective pediatric hemotherapy. Despite the availability of several clinical guidelines for transfusion practices, transfusion practice often deviates from these established guidelines, resulting in under and over utilization of blood products.

Pediatric transfusion practice is usually divided into two periods: (1) neonates from birth through 4 months and (2) older infants (> 4 months) and children. The transfusion in the fetus (in utero) is the domain of obstetric transfusion medicine, while pediatric health care providers are primarily concerned with postnatal transfusion practices involving neonates, infants and children. It is equally important for neonatologists to understand transfusion concerns during the antenatal period as well, as some of the specialized transfusion requirements in postnatal period overlap with those of antenatal period.

TRANSFUSION PRACTICES IN ANTENATAL PERIOD

Intrauterine transfusion (IUT) of red blood cells is indicated most commonly when a fetus is severely anemic due to red cell antigen incompatibility (usually RhD) with maternal blood. IUTs are generally performed by the intravascular route (umbilical vein) or intraperitoneal or combined approach. Infants who received IUT for hemolytic disease of fetus and newborn (HDFN) may have prolonged postnatal transfusion requirement. Erythropoietin has been shown to improve hemoglobin (Hb) and reduce transfusion volume in infants who have a persisting transfusion requirement following IUT. In severe HDFN, IUTs are administered to fetus to prevent or reverse hydrops fetalis and prevent fetal death. IUTs suppress compensatory erythropoiesis in the fetus and after one or more IUTs most of fetal blood is of donor origin. IUT with red blood cells (RBC) lacking the offending antigen is the lifesaving procedure although the treatment is not without risk. Additional maternal red cell antibodies are often formed after IUTs, which can complicate subsequent pregnancies and future transfusions.

The blood for possible IUT must be antigen negative for the offending antibody (generally O RhD negative) and cross-matched against the mother's serum to help rule out any other possible hemolytic antibodies. Additionally, the unit of red blood cells should be cytomegalovirus-negative or leukodepleted, irradiated to prevent transfusion associated graft versus host disease (TA-GVHD), preferably less than 5–7 days old and hematocrit (Hct) level between 70–85%. The rate for red cell IUT is about 5–10 mL/min. In general, volume of 30–60 mL/kg of nonhydropic fetal weight is transfused because volumes higher than this may be difficult for the fetus to tolerate. Once the transfusion is accomplished, a final blood sample is often taken to estimate

the final Hct value of the fetus. If the initial Hb/Hct value is extremely low, a repeat procedure may be necessary within a week. Otherwise, the procedure can be performed every 2–4 weeks based on the post-transfusion Hb value. Intrauterine platelet transfusion procedures are performed to treat fetal thrombocytopenia due to platelet alloimmunization. When fetal platelet count is less than $30 \times 10^9/L$ at 22 weeks of gestation, platelets together with intravenous immunoglobulin at 1 g/kg body weight are administered.

TRANSFUSION PRACTICES IN INFANTS LESS THAN 4 MONTHS OF AGE

Most preterm infants with birth weight of less than 1000 g will require RBC transfusion. Whole blood may be requested for infants undergoing exchange transfusion or massive transfusion, however, RBC along with plasma components or reconstituted whole blood is now increasingly used in many centers.

Red Blood Cell Transfusion

The increased transfusion need in the first four months of life usually arises from: (1) iatrogenic blood loss due to frequent blood sampling; (2) hemolytic disease of newborn; (3) physiologic anemia of prematurity; and (4) prolonged length of hospital stay for premature infants with very low birth weight. Delayed cord clamping at delivery, minimizing iatrogenic blood loss and judicious use of erythropoietin are some of the strategies that can reduce the need for red cell transfusion.

Neonatal red cell transfusion includes small volume (top up) or large volume transfusions in the setting of exchange transfusion, transfusion in hypotensive shock, transfusion for surgery. The red cell transfusion trigger for small volume transfusion in neonates and infants under 4 months of age can be summarized as: Hb less than 12 g/dL in first 24 hours; Hb less than 12 g/dL with intensive care; Hb less than 11 g/dL with chronic oxygen dependency; Hb less than 7 g/dL in a stable infant; acute blood loss more than 10%; sampling more than 10% blood volume/week.

Most RBC transfusions are small volume and are administered in the first month of life to preterm infants. Fresh red blood cells less than 5–7 days should be transfused due to concern with hyperkalemia in older blood units especially in large volume transfusion and renal failure. Red cell additive saline-adenine-glucose and mannitol (SAGM) is safe for small volume top up RBC transfusions and now increasingly used in large volume transfusions in many centers; however, citrate-phosphate-dextrose (CPD) solution may be preferred over SAGM in case of exchange transfusion as former contains some coagulation factors and albumin in plasma, which may be beneficial for the neonate during exchange transfusion. It is preferable to have dedicated blood aliquots from a unit for serial small volume transfusions to minimize multiple blood donor exposures. The use of pediatric bags (pedipacks) is recommended otherwise sterile connecting device can be used for making small volume aliquots from an adult blood unit without decreasing shelf life of original unit.

Blood for neonatal transfusion is often issued as group O RBC (Hct of 55–60%) with compatible infant Rh type. Alternatively, nongroup O infants may receive nongroup O RBCs if passive maternal anti-A or anti-B is not detected in an infant's plasma. RBC transfusions for infants are issued in bags or syringes may be used if less volume of blood is required. Transfusion should be through a standard blood transfusion set (170–260 μm filter) which holds true for other blood components as well. Where small volumes are drawn into a syringe an appropriate filter should also be used. Small volume transfusion dose is 10–15 mL/kg transfused over 2–4 hours or blood may be transfused intermittently in bolus if

syringed blood is used. Electromechanical infusion devices may be used for slow controlled rate of transfusion in neonatal or pediatric patients. Constant rate syringe delivery pumps can be used for transfusion of red cells through small gauge needles. Syringe pumps are suitable for volumes from 10 mL to 50 mL. Blood aliquots and syringed components expire in 4 hours in an open system due to risk of bacterial contamination. The expected post-transfusion increase in Hb depends upon type of anticoagulant preservative solution (3 g/dL in CPD vs 2 g/dL in SAGM) and Hct of blood.

Small volume transfusions can be given repeatedly over the first 4 months of life without further serological testing, provided that there are no atypical maternal red cell antibodies in the maternal/infant plasma, and the infant's direct antiglobulin test is negative, as the development of antibodies to red cell antigens is very uncommon in the first 4 months of life. Leukodepleted blood (residual leukocytes $< 5 \times 10^6$) is generally accepted as equivalent to CMV seronegative component.

Exchange transfusion (ET) in the neonate represents a massive transfusion (> 25 mL/kg) involving the replacement of one or two whole blood volume. Whole blood or reconstituted whole blood can be used for ET. Irradiation of component is desired although not essential. However, irradiation of all cellular components is essential for the neonates with previous IUT. Similarly irradiation is mandatory in following situations: premature neonate with weight less than 1200 g, immunocompromised, receiving blood from relatives or receiving HLA matched or platelet cross-match compatible components. There is no need to irradiate red cells or other cellular components for infants undergoing cardiac surgery unless clinical or laboratory features suggest co-existing immunodeficiency which can put them at risk. Blood for ET and IUT should be transfused within 24 hours of irradiation. Hematocrit of packed red blood cells (PRBC) is lower (50–55%) compared to top up transfusions. Units should not be transfused straight from refrigerator but rather brought to the room temperature before transfusion. When possible, use of a blood warmer is recommended for rapid or massive transfusion. Washing of red cells by manual or automated methods may be desired in selected cases, for example, washing of irradiated red blood cells for prevention of hyperkalemia, allergic reactions to plasma proteins.

A unique situation which affects about 5% of all newborns during the first week is neonatal polycythemia (Hct $> 65\%$) which may lead to hyperviscosity of blood affecting blood flow to many important organs. Whole blood of neonate is removed and replaced with normal saline by partial exchange. Plasma is not used to replace whole blood because necrotizing enterocolitis has been reported as a complication of the use of plasma.

Platelet Transfusion

Thrombocytopenia is one of the most common hematologic abnormalities in the neonatal period with over 75% of episodes occurring in the first 72 hours of life. Early onset severe thrombocytopenia (Platelet count $< 50 \times 10^9/L$) is mainly due to neonatal alloimmune thrombocytopenia (NAIT) and sepsis is responsible for most cases of late onset thrombocytopenia in a preterm infant.

Single unit or aliquots of platelets prepared from whole blood donations, that is, random donor platelets (RDP) or from plateletpheresis donations (single donor platelets; SDP) can be used for correcting thrombocytopenia. Commonly accepted platelet transfusion triggers for infants under 4 months of age are—stable infant with platelet count less than $20 \times 10^9/L$; critically ill preterm infant with platelet count less than $30 \times 10^9/L$; previous major bleed or an active minor bleed in an infant with platelet count less than $50 \times 10^9/L$; platelet count less than $100 \times 10^9/L$ prior to cardiovascular or neurologic surgeries. Even without

thrombocytopenia platelet transfusion is recommended if there is active bleeding in the setting of qualitative defect in platelets or unexplained excessive bleeding in a patient undergoing cardiopulmonary bypass.

Infants should receive ABO and Rh (D) identical platelets as far as possible. Group O platelets should be avoided in non-group O recipients. Plasma volume reduced platelet concentrates may be preferred in selected neonates with fluid restriction. In NAIT human platelet antigen compatible platelets are preferred; however, RDP or even irradiated maternal platelets can be used in emergency. A platelet volume of 5–10 mL/kg raises platelet count of a neonate by $50\text{--}100 \times 10^9/L$. It is recommended to leuko-reduce and irradiate platelet products for use in neonates whenever possible.

Granulocyte Transfusion

Granulocyte transfusions (GT) are rarely performed as there is not enough evidence for benefit of GT in treatment of neonatal infection. GT have been used as adjunct therapy in bacterial sepsis or disseminated fungal infection unresponsive to antibiotics in infants under 2 weeks of age with absolute neutrophil count (ANC) less than $3 \times 10^9/L$ and in infants over 2 weeks of age with ANC less than $0.5 \times 10^9/L$.

Granulocyte concentrates, can be obtained from apheresis procedure or from pooled buffy-coat units derived from whole blood donations. The granulocyte yield is better in leukapheresis compared to buffy coat preparations. The product should be ABO compatible, cross-match compatible with the recipient, CMV seronegative, irradiated (but not leukofiltered). The usual dose is $1\text{--}2 \times 10^9$ neutrophils/kg body weight in a volume of 10–15 mL/kg. Granulocytes should be transfused immediately after collection or stored at 20–24°C without agitation for a maximum period of 24 hours.

Plasma Transfusion

Physiologically low levels of vitamin-K-dependent factors and the contact factors contribute to prolong prothrombin and partial thromboplastin times seen in infants for which fresh frozen plasma (FFP) transfusion is not indicated if there is no bleeding. The justified usage of FFP that are similar to those for older infants and children can be summarized as—coagulation factor deficiency with bleeding, or prior to invasive procedures/surgery if specific factor replacement is not available; replacement therapy in congenital antithrombin III deficiency, protein C or protein S deficiency; clinical evidence of coagulopathy and reversal of warfarin in an emergency situation in a bleeding infant.

Fresh frozen plasma must be compatible with the infant's red cell antigens (group identical or group AB). However, FFP does not need to be Rh-compatible. It is usually transfused in a dose of 10–15 mL/kg for which an adult unit can be split into aliquots. Frozen plasma must be thawed, usually in a water bath, and infused immediately or stored at 1–6°C for up to 24 hours.

Cryoprecipitate is a product derived from the slow thawing of frozen plasma at 4°C that contains predominantly fibrinogen, factor VIII, von-Willebrand factor and factor XIII. Cryoprecipitate is indicated in patients with active bleeding or undergoing an invasive procedure having von Willebrand disease, hemophilia A (when factor VIII concentrates are unavailable) hypofibrinogenemia, dysfibrinogenemia and factor XIII deficiency. It is also given in consumptive coagulopathy when fibrinogen levels are low. Cryoprecipitate should be ABO-compatible with the infant's red cells. A typical cryoprecipitate bag is 10–15 mL in volume which is sufficient to achieve hemostatic level in an infant. It is usually transfused in a dose of 5 mL/kg. Thawed cryoprecipitate is kept at

Table 1 An overview of technical aspects of hemotherapy for small volume transfusions in neonates and infants (modified from AABB)

Component	Dose	Expected rise	Component administration*	Special consideration
Red blood cells	10–15 mL/kg	2–3 g/dL in hemoglobin	Standard blood administration (BA) set	Leukodepleted, irradiated if previous IUT or at risk candidate
Platelets	5–10 mL/kg	50–100 × 10 ⁹ /L in platelet count	Standard BA set or platelet administration set	Leukodepleted, irradiated if previous IUT or at risk candidate
Granulocytes	10–15 mL/kg (1–2 × 10 ⁹ neutrophil)	Variable increase in ANC, clinical response	Standard BA set	Irradiated but no leukodepletion by filtration
Fresh frozen plasma	10–15 mL/kg	15–20% in factor levels	Standard BA set	Nil
Cryoprecipitate	5 mL/kg (usually single unit)	60–100 mg/dL in fibrinogen level	Standard BA set or cryoprecipitate infusion set	Nil

* In infants standard blood administration sets with 170–260 micron filter may be used; however, pediatric blood administration set with integral 3-way tap should be preferred for small volume transfusion. Similarly platelet administration sets having smaller priming volume are to be preferred over standard set if available.

room temperature and should be transfused as soon as possible after thawing.

A summary of practical aspects of transfusion for various blood components can be found in **Table 1**.

TRANSFUSION IN INFANTS MORE THAN 4 MONTHS OF AGE AND CHILDREN

The principles of transfusion support and transfusion needs for older infants and children are similar to those for adults, though recipient's blood volume is still an important issue while administering blood products in older infants. However, unlike neonates, there is no concern over choice of anticoagulant preservative solution in the blood. Serum grouping for ABO confirmation is required in this group unlike in infants less than 4 months of age. Serological testing is mandatory after each transfusion including screening for the presence of clinically significant antibodies. Neonates rarely develop febrile non-hemolytic transfusion reactions with less chances of alloimmunization; however, children can have adverse reactions due to leukocytes if blood unit is not leukodepleted and easily form red blood cell alloantibodies.

Children can tolerate lower hemoglobin levels without symptoms as compared to adults thus a lower transfusion trigger may be preferred in many children. Most transfusions are required for children with hemoglobinopathies, coagulopathies, bone marrow failure syndromes, hematological malignancies, transplants, surgeries and massive blood loss. Red cells are indicated for correction of significant preoperative anemia, acute blood loss with hypovolemia, intraoperative blood loss of more than 15% of blood volume, Hb less than 8 g/dL in perioperative period/chemotherapy/congenital or acquired symptomatic chronic anemia, Hb less than 13 g/dL with severe cardiopulmonary disease. The volume for red blood cell transfusion in children can be calculated as below: Volume (mL) of RBC to be transfused = Desired Hb rise (g/dL) × weight (kg) × 3.

Thalassemia and hemophilia are two important inherited disorders which are traditional users of red blood cells and plasma products respectively. Sick cell disease, which is prevalent in central and western India also puts burden on the limited blood resource. Patients with sickle cell disease are managed with top up and exchange transfusion with red blood cells. Thalassaemic patients are managed with regular PRBC transfusions along with chelation therapy; however, blood transfusion is not without risks in this population. Many patients develop acute and chronic adverse effects of blood transfusion. In thalassemia, a pretransfusion Hb of 9–10 g/dL should be maintained. All patients in this age

group who are transfusion dependent should be phenotyped for red cell antigens other than ABO and RhD (extended red cell phenotype) as soon as possible to minimize red cell alloantibody production and provide compatible units in the event of formation of alloantibodies. Similarly Hepatitis B vaccination should be initiated for children who are candidate for chronic transfusions.

Bone marrow transplant (BMT) is a specialized procedure which is performed mainly in children with leukemia, lymphoma, aplastic anemia and thalassemia. In allogeneic BMT when recipient and donor are of different ABO and Rh blood groups a new protocol on the specifications and selection of blood products is followed. Irradiated and leukodepleted blood components are mainstay of treatment in BMT. Post-transplant children and adult patients should continue to receive irradiated blood components until the patients have recovered immunologically.

Cryoprecipitate and FFP transfusions may be used for treatment for hemophilia A and B patients if factor concentrates are not available, however, hemophilia patients should preferably be treated with plasma derived/recombinant factor concentrates. The indications and selection of platelets and plasma components in children are based on transfusion practices used for adults. Due to larger body weight doses for blood components are different from that of neonates. Thus the platelet dose for children over 10 kg body weight is 1 unit of RDP/10 kg weight or 10–15 mL/kg. Similarly minimum granulocyte dose for larger children is 1×10^{10} cells/kg.

Massive transfusion can cause dilutional thrombocytopenia and coagulopathy, which may require large quantities of platelet and plasma components. Use of rFVIIa may be considered in patients where bleeding is uncontrolled by conventional blood components.

Platelet transfusions are indicated especially in aplastic anemia, acute leukemia, hemopoietic stem cell transplant, platelet function disorders, massive transfusion, consumptive coagulopathy and immune thrombocytopenia. Immune thrombocytopenic purpura (ITP) is among the most frequent causes of childhood thrombocytopenia. Platelets are only indicated in patients with ITP who are having major, life-threatening bleeding. Platelets are generally not indicated in thrombotic thrombocytopenic purpura and heparin induced thrombocytopenia.

The decision to transfuse any blood component in a pediatric patient requires critical clinical evaluation supported by laboratory investigations. Newer viscoelastic tests of coagulation, for example, thromboelastography may be used especially during perioperative period in guiding the component use in children. However, guiding principle in blood component therapy should be to achieve a clinical goal rather than to correct abnormal laboratory values.

IN A NUTSHELL

1. The principles of transfusion support for children and adolescents are similar to those for adults.
2. Younger infants have many special transfusion considerations, which have been outlined here namely: syringed components, relatively fresh blood, CMV safe/leukodepleted blood components, irradiated cellular components, red cells with high hematocrit, volume reduced blood products and aliquoting of a blood unit.
3. Although it may not be possible to meet all the *special* requirements for blood components in a pediatric patient, every effort should be made to provide the safest and most effective transfusion.
4. There are many patient characteristics, e.g., age, weight, diagnosis, procedure and severity of illness that contribute to the likelihood of receiving a blood component therapy in pediatric populations.
5. Each pediatric center should have own manual or standard operating procedures for guiding clinical practice.

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Chapter 38.25

Stem Cell Transplantation

Mammen Chandy

Hematopoietic stem cell transplantation (HSCT) is widely used to treat various malignancies and a number of hematologic, immune and genetic diseases. The annual rate of allogeneic HSC transplants now exceeds 40,000. HSCT is an effective treatment for acute leukemias and bone marrow failure syndromes such as aplastic anemia and myelodysplastic syndromes. In thalassemia major, HSCT now provides a cost effective alternative to transfusion/chelation therapy (**Box 1**). Graft versus host disease, interstitial pneumonia, leukemic relapse and infection remain the major complications.

TYPES OF STEM CELL TRANSPLANT

Allogeneic Transplant

Where the donor is a histocompatible sibling or family member (related) or from a donor registry (unrelated), it is allogeneic transplantation. Another source can be umbilical cord blood, which is a rich source of hematopoietic stem cells. This is illustrated in **Figure 1**. The bone marrow and immune system of patient who has a human leukocyte antigen (HLA) matched donor is destroyed (this is called conditioning) and the stem cells of the donor are harvested either from the bone marrow or the peripheral blood and transfused.

Syngeneic Transplant

In this type, donor is an identical sibling. These transplants are easier to perform because engraftment is faster and graft versus host disease (GVHD) is rare, and if present, mild. However, relapse is much higher in syngeneic transplants for leukemia because there is no graft versus leukemia effect.

Autologous Transplant

Here, the patient acts as his own donor. Usually done in diseases where the marrow is free of tumor and the dose limiting toxicity of chemotherapy is marrow suppression. The patient's own marrow can be harvested, cryopreserved and then returned back after ablative chemotherapy (**Fig. 2**). In some situations, the marrow will be treated (purging) with either drugs or monoclonal antibodies to remove any minimal tumor in the harvest.

Graft Source

Bone marrow has traditionally been the graft source but increasing number of transplants are being done with mobilized peripheral blood stem cells (PBSCT), however, because of larger number of T-cells there is some increase in chronic graft versus host disease. The stem cells can be *pushed* into the peripheral blood using growth factors or a mobilizing agent called preixafor. Alternatively cyclophosphamide is given and as the counts are rising, there is an increase in number of stem cells in the peripheral blood which can be harvested using a cell separator.

The Donor

Once the decision to have a bone marrow transplant has been made, the next step is to perform HLA typing on the patient, sibling and parents. Most centers would perform a transplant only if a full six antigen HLA A, B and DR matched related donor is available. Bone marrow transplantation can be done even if the donor and recipient are not ABO blood group matched unlike solid organ transplants. If there are no matched siblings who can serve as a donor then an extended family search can be done in which

BOX 1 Indications for allogeneic transplantation

- **Malignant diseases:**
 - Acute myeloid leukemia—presence of > 15% blasts after 1st course of chemotherapy, absence of favorable genetic abnormalities, presence of adverse genetic abnormalities, e.g., -5, -7, del (5q)
 - Acute lymphoblastic leukemia (ALL)—high risk ALL in CR1, early relapsed ALL in CR2
 - Juvenile chronic myeloid leukemia
 - Lymphomas
- **Bone marrow failure:**
 - Severe aplastic anemia, Diamond-Blackfan anemia, Fanconi anemia, myelodysplastic syndromes
- **Genetic disorders:**
 - *Immune:* Severe combined immunodeficiency
 - *Granulocyte disorders:* Kostmann syndrome, chronic granulomatous disease, Chediak-Higashi syndrome
 - *Platelet disorders:* Wiskott-Aldrich syndrome, Glanzmann thrombasthenia
 - *Red cell disorders:* Thalassemia major, sickle cell disease
 - *Enzyme deficiency disorders:* Gaucher disease, leukodystrophies, Lesch-Nyhan syndrome, etc.
 - Osteopetrosis.

Abbreviation: CR, complete remission

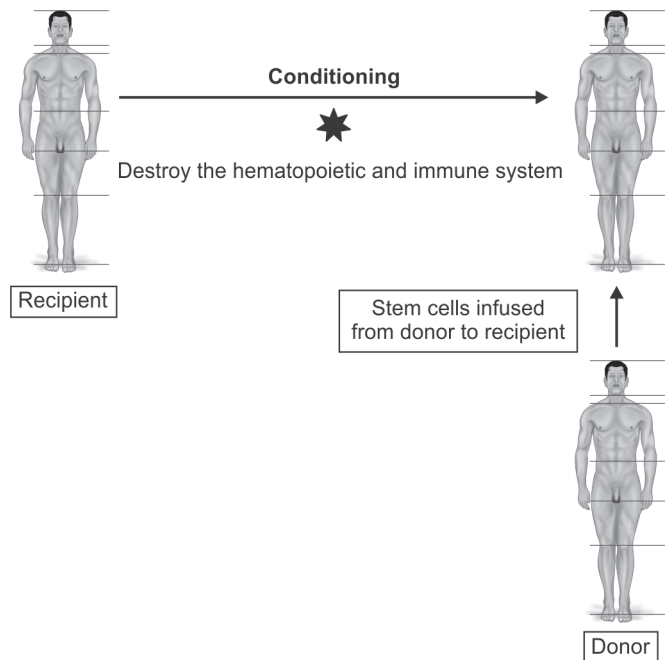


Figure 1 Principle of an allogeneic stem cell transplant

parents or cousins are tested but the probability of finding a donor is small except where the parents are consanguineous. If there is only one child then the family can plan to have another child and HLA typing can be performed on the DNA sample that has been obtained from a chorionic villus sample. When this child is born either a cord blood transplant can be done or a regular transplant can be done when the baby is 2 years old.

TRANSPLANT PROCEDURE

At the time of transplant the patient and donor undergoes a series of tests after which the patient is admitted to the ward. The patient is then taken to the operating room where a dual lumen Hickman catheter is inserted under anesthesia: this catheter is

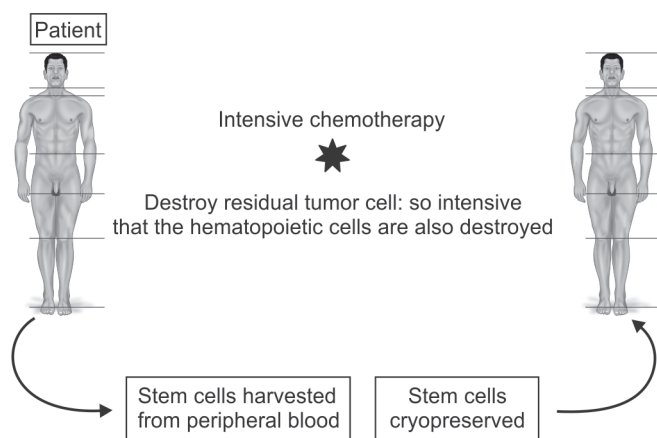


Figure 2 Principle of an autologous stem cell transplant

used thereafter for blood tests, transfusions and administration of medication and fluids. It is removed when the patient is ready to go home. The catheter is dressed twice weekly and flushed with heparin saline when not in use. The patient is transferred to the bone marrow transplant unit prior to initiation of the conditioning regimen and is kept in the positive pressure HEPA (High efficiency particulate air) filtered unit till engraftment has occurred and the absolute neutrophil count is over 500/cu mm. The HEPA filters are high efficiency filters with a size of 0.3 microns and a trapping efficiency of 99.97%. The air quality is monitored using air quality monitors and air pressures are assessed using a pressure-testing device. Settle plate cultures are also done every month to look for microbiological contamination.

Conditioning

This refers to the treatment given to the patient, which permits engraftment of donor marrow and involves the creation of space by destroying the patient's own marrow (cytoreduction) and immunosuppression to prevent rejection. The choice of conditioning regimen for a given patient is dictated by the underlying disease and donor characteristics. Most transplant centers use chemotherapeutic agents alone for conditioning; busulfan orally at a dose of 16 mg/kg over 4 days is administered followed by cyclophosphamide 50 mg/kg for 2–4 days. Intravenous busulfan is better tolerated and has more predictable pharmacokinetics. Total body irradiation 12 Gy over 3 days is often used for transplant conditioning in patients with acute lymphatic leukemia. In patients with a high risk of rejection such as thalassemia, antilymphocyte globulin may be added to the conditioning regime. In diseases such as aplastic anemia, where the rejection rate is increased, fludarabine is added to the conditioning regime. Fanconi anemia because of the increase sensitivity to chemotherapeutic agents requires special conditioning with reduced doses. Older patients with comorbidities are nowadays conditioned with non-myeloablative or reduced intensity conditioning (RIC) regimens. Here, drugs such as fludarabine are used to suppress the patient's immune system enough to allow engraftment of donor cells and this suggests that it is not necessary to destroy the marrow and create *space* for the donor stem cells.

Bone Marrow Harvest

The donor is admitted a day or two before the harvest. Under general anesthesia marrow is aspirated from the iliac bone using either a harvest needle or even with a sternal aspirate needle. There is no surgical incision. The volume of marrow harvested is dependent on the weight of the patient: a nucleated cell dose of

300 million-marrow cells/kg (3×10^8) of the recipient is required. If the donor is over 25 kg, 8 mL/kg of blood is collected and used as an autologous transfusion during the harvest. If autologous transfusion is not feasible then and the harvest volume is large, irradiated leukodepleted blood is transfused. The donor is discharged the day after the harvest.

Stem cells can also be collected from the donor using an apheresis machine after administration of G-CSF for 4–5 days and this is called a PBSCT. Engraftment is faster following a PBSCT as compared to bone marrow transplantation (BMT) but the incidence of chronic GVHD is also greater with PBSCT. In certain situations such as high-risk leukemia, chronic GVHD can lead to a potential graft versus leukemia effect thus translating to higher cure rates with PBSC than with bone marrow transplant.

The harvested cells are usually not treated and are directly infused into the patient like a blood transfusion. If the patient and donor have different blood groups, the harvest may need to be red cell depleted either using hydroxyethyl starch or using a cell separator.

Transplant

The harvested marrow looks just like blood and is infused to the donor like a blood transfusion. Following the infusion of donor marrow the stem cells home in to the patient's marrow and a rising white cell count over the next 15 days is evidence of engraftment. One may use colony stimulating factors (G-CSF, GM-CSF) to hasten engraftment in sick patients. Red cell genotyping, cytogenetics or DNA fingerprinting will be used post BMT to document engraftment and to look for residual disease. Prior to transplant, the patient and donor DNA is tested using a set of VNTR's to look for specific DNA patterns and this is used post-transplant to see if the hematopoietic cells being produced belong to the donor. The patient is considered to be a full chimera if all the cells in the blood are donor in origin and a mixed chimera if residual host cells are present. Usually patients achieve full donor chimerism 30–45 days following BMT if a myeloablative conditioning protocol is used. The patient is transferred out of the BMT unit when his neutrophil count is over 500/cu mm and discharged when there are no IV medications to be administered.

COMPLICATIONS

Graft versus host disease, infection and regimen related toxicity are the major acute complications of BMT. The late complications include relapse, sterility, cataract and second malignancies (**Box 2**).

BOX 2 Complications following hematopoietic stem cell transplantation

- Acute complications
 - Acute graft versus host disease
 - Infections
 - Graft rejection
 - Veno-occlusive disease
 - Hemorrhagic cystitis
 - Interstitial pneumonia
- Chronic complications
 - Chronic graft versus host disease
 - Relapse
 - Sterility
 - Cataract
 - Second malignancy.

Graft Versus Host Disease

This is one of the most devastating complications of BMT and is termed acute if it occurs in the first 100 days following

transplantation and chronic if it continues or develops after this period. Despite a six-antigen HLA match, the donor T lymphocytes on entry into the patient may recognize minor differences in the recipient's cells, recognizing them as foreign and attack the recipient. Any organ in the body may be affected but the skin; intestine and liver usually bear the brunt of the attack by the donor lymphocytes in acute GVHD. Generalized erythema, maculopapular rash involving palms and soles and in severe cases toxic epidermal necrolysis (TEN) are the main cutaneous manifestations. Intestinal involvement usually manifests as diarrhea while upper gastrointestinal involvement may manifest with vomiting and loss of appetite. Progressive jaundice with minimal elevation of enzymes is seen in hepatic GVHD. Severe GVHD is associated with delayed engraftment and increased propensity to infections particularly with cytomegalovirus (CMV). Acute GVHD develops in 30–60% of patients transplanted with HLA identical marrow and may be an indirect cause of death in 20–30% of affected individuals. Acute GVHD is graded I–IV based on the degree of target organ involvement. Increased host age and transplants from female donors to male recipients particularly if the female is multiparous increases the risk of GVHD.

Chronic GVHD produces a picture similar to scleroderma. In the skin, manifestations range from dry patches or areas of variegated pigmentation to extensive dermal scarring that produces thickened atrophic skin. The GI tract involvement may result in lichenoid lesions in the oral mucosa, xerostomia, dysphagia, diarrhea or malabsorption. Chronic GVHD of the liver usually presents as a cholestatic process, which can progress to a syndrome similar to primary biliary cirrhosis. The other manifestations include sicca syndrome, pulmonary dysfunction and development of autoantibodies. Chronic GVHD is graded as either limited or extensive.

The standard protocols use a combination of 2 drugs, methotrexate and cyclosporine, as prophylaxis for GVHD. Methotrexate is given as an intravenous push in 3–4 doses over the first 10 days following BMT. Cyclosporine is continued for a period of 6–12 months depending upon the disease and the presence of GVHD. This is unlike solid organ transplantation where the drug has to be continued lifelong. Once GVHD develops the main stay of treatment is with corticosteroids. In refractory cases, antithymocyte globulin (ATG), OKT3, mycophenolate, sirolimus and IL2 antibody may be used. Chronic GVHD is managed with prednisolone along with cyclosporine.

Infection

In the initial period following transplantation, profound neutropenia, disruption of anatomic barriers secondary to mucositis and presence of central venous catheters are the most important risk factors resulting in bacterial and disseminated fungal infections with *Aspergillus* and *Candida*. At the earliest sign of infection or fever the patient is started on intravenous antibiotics depending on the sensitivity patterns in the center: piperacillin, tazobactam and amikacin are the usual first line. If there is persistent fever, carbapenems such as imipenem or meropenem and glycopeptides such as vancomycin or teicoplanin are added. With the increasing incidence of carbapenem resistant organisms colistin is added. Prophylactic posaconazole is used and when the patient is not able to tolerate orally this is changed to caspofungin or amphotericin.

Viral infections with herpes, CMV and adenoviruses contribute to the morbidity and mortality of transplantation after engraftment. The presence of GVHD, high intensity of immunosuppression, manipulation of the graft (T cell depletion) and use of fludarabine/ampath (anti-CD45 monoclonal antibody) as part of conditioning are the risk factors for CMV and adenovirus infections. CMV infection commonly targets lungs, liver and intestine. CMV

quantitative polymerase chain reaction is done at 4 weeks and every 2 weeks thereafter. Pre-emptive treatment with ganciclovir is started if the titer is greater than 1,000. The most common manifestation of adenovirus infections is hemorrhagic cystitis, gastroenteritis, pneumonia and liver cell failure. Treatment options are limited with anecdotal reports of success using cidofovir. Patients with chronic GVHD are immunosuppressed and remain at risk for infections with encapsulated organisms such as *Pneumococcus*, *Meningococcus* and *Pneumocystis jirovecii*. Prophylactic penicillin and trimethoprim-sulfamethoxazole in the first year post-transplant is useful in reducing the incidence of these infections.

Interstitial Pneumonia

This complication is observed in 30% of patients where radiation is used for the conditioning and can be crippling. In transplants where radiotherapy is seldom used, busulfan related lung damage, GVHD, CMV and *Pneumocystis jirovecii* are other etiologic agents that have to be considered.

Regimen-related Toxicity (RRT)

Veno-occlusive Disease of the Liver

Veno-occlusive disease of the liver (VOD) is a major problem with conditioning regimens containing busulfan and cyclophosphamide. It is characterized by weight gain, ascites and tender hepatomegaly, which appears within the first week after transplant and usually resolves by the third week. If severe, it can progress to hepatic failure and death. Treatment is supportive with careful fluid management. Defibrotide, recombinant tissue plasminogen activator (tPA) and heparin have also shown some benefit but the latter two carry a risk of hemorrhage. Prophylactic strategies including ursodeoxycholic acid and heparin have been evaluated, but neither has shown consistent benefit. In iron overloaded patients cardiac failure and acute pericardial tamponade can occur.

Hemorrhagic Cystitis

It is a well-known complication of cyclophosphamide but can also arise from infection with adenovirus or BK virus. This is prevented by hydration and MESNA. Severe cases may require continuous bladder irrigation, cystoscopy and clot evacuation. BK virus infection is best treated by reducing the immunosuppression: drugs like ciprofloxacin, leflunomide and cidofovir can be used.

Graft Failure

Graft failure is defined as failure to achieve neutrophil recovery (absolute neutrophil count > 500 per mm^3) by day + 30 after transplant. It results from eradication of the incoming donor cells by recipient's immune system. The risk factors include inadequate conditioning, inadequate cell dose, T cell depletion of the donor cells and HLA disparity between donor and recipient. With appropriate conditioning regimens graft failure is rare.

ABO Mismatched Transplants

ABO identity is not essential for BMT unlike solid organ transplants since stem cells do not carry ABO antigens. Removal of red cells from the harvested marrow with cell separators or gravity sedimentation with hydroxyethyl starch is all that is necessary in order to prevent hemolysis during infusion of the marrow in a group-mismatched transplant. It is much more difficult to remove ABO antibodies from the patient's plasma by plasmapheresis or immunoabsorbent columns. Delayed red cell engraftment can occur in about 20% of major ABO mismatched transplants but most patients recover as the recipient's immune system is replaced by the donors.

Blood Support

Aggressive blood and blood component support is crucial during the mandatory period of aplasia, while awaiting marrow recovery. Red cell transfusions are given to keep the hemoglobin levels above 9 gm% (PCV 27%) and platelets transfusions given to maintain a platelet count above $10 \times 10^9/L$. All blood products are irradiated to prevent transfusion associated GVHD. When possible, the blood should be leukodepleted centrally if that is not possible, leukocyte filters are recommended. Pall filters are used to leukodeplete red cells and platelet products and usually deplete the leukocyte load by 3–4 logs.

POST-TRANSPLANT CARE

Following a bone marrow transplant for a patient who has no graft versus host disease, cyclosporine is given at full doses for six months after which it is tapered and stopped 1 year post-transplant. The tapering is done earlier for malignant diseases. *Pneumocystis jirovecii* prophylaxis and supplemental folic acid is given for 1 year. The child or adult can return to normal activities within 6 months after a transplant and the quality of life is excellent. Most patients do not require any special treatment or care 1 year post-transplant unlike solid organ transplants, where they are on life-long immunosuppression with its associated complications and high cost.

Immunization

All children who have received allogeneic HSCT should be considered for reimmunization program. It should commence 12 months after a HLA-identical sibling donor transplant: this is delayed if there is graft versus host disease (**Table 1**). Child should be off all immunosuppressive treatment including steroids and cyclosporine and should not have evidence of active or chronic GVHD.

AUTOLOGOUS TRANSPLANTATION

Autologous stem cell transplantation (ASCT) is widely used in pediatric malignancies (**Table 2**). The rationale for this treatment is that dose intensification of chemotherapeutic agents increases the response rate of chemo sensitive tumors and if hematopoietic

toxicity is a limiting factor, stem cells are harvested, cryopreserved and reinfused after the chemotherapy is given. Autologous stem cell transplant requires that the patient should be in remission or have minimal disease at the time of transplant.

ALTERNATE DONOR TRANSPLANTATION

Allogeneic transplantation requires the presence of a 6 antigen matched HLA-identical donor. The chances that a sibling will be 6 antigens identical are around 25% and this improves to 30–40% using an extended family search. This means that a large number of patients who require a transplant will not find a HLA identical donor within the family. In this situation, the options of transplant and donor source include

- Matched unrelated donor (MUD)
- Cord blood transplants (CBT)
- Haploidentical transplants.

These transplants may be associated with slower engraftment, higher rejection rates and higher incidence of GVHD and hence necessary modifications in conditioning protocols and manipulation of stem cells may be required to make the transplant a successful one. However, today the results of alternative donor stem cell transplants are improving to the point that they are not inferior to matched related transplants.

Matched Unrelated Donor (URD) Transplants

The absence of a HLA identical sibling donor and the necessity for BMT has led to the formation of a number of bone marrow donor registries around the world. These registries maintain detailed HLA records of donors who are immediately accessible on request. It is estimated that approximately 22 million donors are registered in marrow donor registries around the world thus forming a large donor pool. Once a donor search is initiated, the initial reports of donors identified all over the world may be available within 5–7 days and a single donor is identified subsequently after high resolution HLA molecular typing is done. The average time from initiation of a donor search to transplant can vary between 1–6 months depending upon the country and the marrow registry. The bone marrow is usually harvested in the country where the donor is a resident (usually in a hospital recognized by the Registry) and then transported to the country/place where the patient has

Table 1 Post-HSCT immunization schedule

a. Mandatory 1 year			
1. Tetanus toxoid 0.5 mL IM	0 month	2 months	4 months
2. Inactivated polio vaccine 0.5 mL IM	0 month	2 months	4 months
3. <i>Haemophilus influenzae B</i>	One dose		
4. Pneumococcal vaccine (23 valent)	One dose		
Tetanus and polio vaccines are to be given simultaneously. <i>Haemophilus influenzae</i> and pneumococcal vaccines are to be given 1 month apart, starting 1 month after initiation of the tetanus and polio vaccination.			
2 years			
No graft versus host disease/not on immunosuppression			
1. Measles/Mumps/Rubella	One dose		
b. Optional after 1 year			
1. Hepatitis B			
2. Typhoid			
3. Cholera			
4. Rabies (if indicated)			

Table 2 Diseases treated with autologous stem cell transplantation

Neuroblastoma	Stage 2–4, at any age with <i>MYCN</i> amplified tumor Stage 4 disease in children over 1 year of age Relapse
Soft tissue sarcoma	Primary refractory disease Stage 4 disease at diagnosis
Ewing tumor	> 10% viable tumor in the resected tumor after induction therapy Relapse
Wilms tumor	Primary refractory disease Relapse in case of unfavorable histology 2 or more relapses
Brain tumor	Medulloblastoma in CR2 PNET in CR2
Lymphoma	Non-Hodgkin and Hodgkin lymphoma in second CR
Multiple myeloma	This is the most common indication in adults

Abbreviations: CR, complete remission; PNET, primitive neuroectodermal tumor

been conditioned for transplant. With recent improvements in HLA typing, conditioning regimens and supportive care, MUD transplants in acute leukemia offer as good a chance of cure as with HLA identical sibling transplants.

Cord Blood Transplant

Cord blood is a rich source of hematopoietic cells and because of their increased proliferative capacity, a 1 log lower cell dose is adequate for transplantation. Since the T cells in cord blood are immunologically naïve stringent, HLA matching is not essential and there is a low incidence of GVHD in cord blood transplants (CBT). This has led to the development cord blood banks (UCB) where cord blood units are stored and made available for transplantation. UCB offers the advantage of significantly faster availability of banked cryopreserved UCB units compared with unrelated donor stem cells.

Umbilical cord blood stem cells are the preferred donor source for children who need a stem cell transplant and do not have a matched related donor. In children with acute leukemia the results of CBT are in fact superior to matched related donor transplants particularly if the, cord blood match is good and the cell dose is high. However, in nonmalignant diseases particularly thalassemia and aplastic anemia where the risk of rejection is high, cord blood may not be the preferred donor sources.

Haploidentical Transplant

Virtually all patients who need a stem cell transplant, have at least one haploidentical parent sibling or cousin who could serve as a donor. Originally these transplants were done using mega doses of stem cells to avoid rejection and T-cell depletion to reduce GVHD. However, T-cell depleted grafts are associated with delayed immune reconstitution and associated infections and relapse. T-cell depletion is also expensive and requires specialized equipment. The John's Hopkins group has shown that it is possible to do a T-cell replete transplant using either bone marrow or peripheral blood stem cells and destroy alloreactive T cells by administering large doses of cyclophosphamide on day 3 and 4 after graft infusion. The results are promising but relapse still remains a problem.

BONE MARROW TRANSPLANTATION FOR INDIA

For a developing country like India, it would seem irrational to develop such high technology medical treatment that is likely to benefit only a few when there are more urgent health priorities competing for scarce resources. The current cost of bone marrow transplantation in the United States is about \$150,000 (INR 1 crore). It is possible to transplant patients in India at a cost of about INR 8–12 lakh. The costs involved in alternate donor transplantation will be much higher and can vary between INR 20–25 lakh depending on the type of transplant. These costs will still be much lower than if the patient traveled abroad for a transplant. There are approximately 37 transplant centers in Indian performing allogeneic and autologous transplants and 1,000 transplants were performed in India in 2013. (Data from the Indian Stem Cell Transplant Registry). Inadequate resources and lack of trained personnel are some of the reasons why transplant activity in India is far below current practice in most developed countries. The practice of private cord blood banking should be discouraged and the government should help establish public cord blood banks in India. Hematopoietic stem cell transplantation should be developed in India since it will save valuable foreign exchange, upgrade the quality of medical care in tertiary referral institutions and provide a lifesaving treatment for the patient in his own country.

IN A NUTSHELL

1. Hematopoietic stem cell transplantation is well established technique and is being used for multiple malignant and benign hematological disorders.
2. Commonly used stem cell transplants include allogenic, syngenic and autologous.
3. Current advances in conditioning regimens transplant procedure and advances in management its complications have greatly improved the long-term survivals.
4. The donors for allogenic stem cell transplant are usually available for 30% of cases. Therefore alternative sources of donor for transplantation are being considered which include
 - Matched unrelated donor
 - Cord blood transplants
 - Haploidentical transplants
5. Initially the transplants from alternative donor had slower engraftment higher rejection rate and high incidence of GVHD.
6. Necessary modifications in conditioning regimens and manipulation of stem cells have greatly improved the long-term survivals in patients undergoing stem cell transplantation from alternative donor sources.

MORE ON THIS TOPIC

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Chapter 38.26

Myelodysplastic Syndromes

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Myelodysplastic syndrome (MDS) comprises of a heterogeneous group of bone marrow (BM) disorders resulting from a clonal stem cell defect characterized by cytopenia despite a relatively hypercellular marrow, ineffective hematopoiesis, morphological dysplasia in the marrow elements, no response to hematinics such as iron, B12 or folic acid and risk of progression to leukemia. MDS in childhood is extremely rare and accounts for less than 5% of all hematopoietic neoplasm in children below the age of 14 years. Differences between adult and childhood MDS are depicted in **Table 1**.

CLASSIFICATION

Myelodysplastic syndrome is classified as primary or secondary. About one-fifth of children with primary MDS may have an underlying genetic defect that predisposes them to develop MDS at a young age. Secondary MDS occurs in patients after chemotherapy or radiation therapy; in such cases it is known as therapy-related MDS or (t-MDS). It may also occur in patients with inherited BM failure disorders, acquired aplastic anemia, or familial MDS. Among the inherited BM failure disorders, 47% of Fanconi anemia patients progress to MDS and acute myeloid leukemia (AML) and 10–25% of patients with Shwachman-Diamond syndrome progress to MDS. However, patients of dyskeratosis congenita hardly ever progress to MDS. Genetic disorders like Down syndrome (DS), Noonan syndrome and neurofibromatosis can also lead to secondary MDS. A clinical classification of myelodysplastic and myeloproliferative diseases in children is shown in **Box 1**. Specific subtypes are discussed in detail below.

BOX 1 Categories of myelodysplastic and myeloproliferative diseases in children

- I. *Myelodysplastic/Myeloproliferative disease*
Juvenile myelomonocytic leukemia (JMML)
- II. *Down syndrome (DS) disease*
Transient abnormal myelopoiesis (TAM)
Myeloid leukemia of DS (ML-DS)
- III. *Myelodysplastic syndrome (MDS)*
Refractory cytopenia (RC) (PB blasts < 2% and BM blasts < 5%)
Refractory anemia with excess blasts (RAEB) (PB blasts 2–19% or BM blasts 5–19%)
RAEB in transformation (RAEB-t) (PB or BM blasts 20–29%).

REFRACTORY CYTOPENIA OF CHILDHOOD (RCC)

Refractory cytopenia of childhood is the most common subtype of MDS in children and adolescents, accounting for approximately half of all MDS cases. It affects boys and girls with equal frequency.

Clinical Features

Blood and bone marrow are always affected; spleen, liver and lymph nodes are generally not affected. The most common symptoms are malaise, bleeding, infection and fever. Hepatosplenomegaly is not a feature. In up to 20% of cases there are no clinical signs or symptoms. Majority of patients present with thrombocytopenia, while anemia and neutropenia are noted in 50% and 25% cases, respectively.

Morphological Features

The peripheral blood (PB) smear shows red cell anisopoikilocytosis and macrocytosis. Anisochromia is present. Neutropenia may be severe in 25% cases with pseudo-Pelger-Huet nuclei and/or hypogranularity of neutrophil cytoplasm. Blasts are absent or account for less than 2% of the white cells. Platelets display anisocytosis and giant platelets may be noted and counts are generally less than $150 \times 10^9/L$.

Bone marrow aspirate shows dysplastic changes which may be present in two different myeloid cell lineages, or exceed 10% in one single cell line. Erythroid abnormalities include nuclear budding, multinuclearity, karyorrhexis and internuclear bridging along with megaloblastoid changes. It is important to note that ring sideroblasts are generally not found. Cells of granulocytic series reveal hyposegmentation with pseudo-Pelger-Huet nuclei, hypogranularity of cytoplasm, giant band forms and less than 5% blasts. Megakaryocytes are low in number; detection of micromegakaryocytes favors the diagnosis of RCC.

About 75% of children with RCC show considerable hypocellularity of the BM. Cellularity may be as low as 5–10% of the normal age matched value. There is a moderate increase in erythropoiesis with accumulation of immature precursors, mainly proerythroblasts. Increased numbers of mitosis indicate ineffective erythropoiesis. Granulopoiesis is decreased with less than 5% blasts, which is verified by CD34 staining. Megakaryocytes are decreased in number but may be normal also. Dysplastic changes include non-lobulated nuclei, micromegakaryocytes and abnormally separated nuclear lobes. There is no increase in reticulin fibers. Multiple sections prepared from the biopsy are helpful in identification of abnormal megakaryocytes and immunohistochemistry to identify micromegakaryocytes is obligatory. This is achieved by the expression of platelets glycoprotein like CD61 (GP 111a), CD 41(GP11b/111a) or von Willebrand factor.

Fatty tissue between the areas of hematopoiesis can mimic aplastic anemia and therefore at least two biopsies at least 2 weeks apart are recommended to facilitate the detection of representative BM spaces containing foci of erythropoiesis. Morphological differences between refractory cytopenia of childhood (RCC) and aplastic anemia (AA) in childhood are depicted in **Table 2**. Differential diagnosis which may present with morphological features indistinguishable from refractory cytopenia of childhood is depicted in **Box 2**.

Management

Hematopoietic stem cell transplantation (HSCT) is the only curative therapy and is the treatment of choice with monosomy 7 or complex karyotype early in the course of their disease. An expectant approach with careful observation may be reasonable for patients in the absence of transfusion requirements, severe cytopenia or infections. Immunosuppressive therapy can be a successful therapy strategy for improving outlook in some children with RCC since early BM failure in such cases can be partly mediated by T-cell immunosuppression of hematopoiesis. Preliminary data have shown a few long lasting responses in children with RCC treated with antithymocyte globulin. Whether immunosuppressive therapy can result in sustained responses in childhood RCC is not known.

Prognosis

Most cases of RCC show a normal karyotype irrespective of BM cellularity though monosomy 7 is the most common cytogenetic abnormality. Patients with monosomy 7 have a significantly higher probability of progression than other chromosomal abnormalities or normal karyotype.

Table 1 Difference between adult and pediatric myelodysplastic syndromes (MDS)

Adult MDS	Pediatric MDS
1. Refractory anemia with ring sideroblasts common	1. Refractory anemia with ring sideroblasts extremely rare
2. MDS associated with isolated del (5q) chromosome abnormality are common with good prognosis	2. MDS associated with isolated del (5q) chromosome abnormality are very rare
3. Isolated anemia is the major presentation in refractory anemia (RA) in adults	3. Isolated anemia is an uncommon presentation. Common presentations are thrombocytopenia and neutropenia
4. Bone marrow are mostly hypercellular	4. Hypocellularity of bone marrow more commonly seen
5. RAEB-t (Refractory anemia with excess blast in transformation) has not been retained in adult MDS in the present WHO classifications as these cases behave like AML	5. RAEB-t has been retained in childhood MDS. Children with RAEB-t have stable peripheral blood counts for weeks or months and do not behave as AML
6. RAEB 1 and 2 (Refractory anemia with excess blasts); distinction based on blast percentage in PB/BM has useful prognostic significance	6. RAEB 1 and 2 (Refractory anemia with excess blasts); distinction based on blast percentage in PB/BM has no prognostic significance

Table 2 Morphological differences between refractory cytopenia of childhood (RCC) and aplastic anemia in childhood (AA)

RCC	AA
1. BM biopsy shows patchy distribution of erythropoiesis and increased mitoses with maturation arrest and increased proerythroblasts among at least 20 erythroid precursors	1. BM biopsy may not reveal erythropoiesis or show a single focus with less than 10 cells with maturation to late erythroid stages with no dysplastic changes
2. Decreased granulopoiesis with marked dysplastic changes	2. Decreased granulopoiesis with maturation and no dysplasia
3. Decreased megakaryopoiesis with dysplasia and presence of micromegakaryocytes in BM biopsy	3. Hardly any megakaryocytes in BM biopsy without any dysplasia. No micromegakaryocytes
4. CD34 positive blasts may be seen in the BM biopsy	4. Blasts are not present in the biopsy specimen

BOX 2 Differential diagnosis which may present with morphological features indistinguishable from refractory cytopenia of childhood

Infections: Cytomegalovirus, herpes virus, parvovirus B19, visceral leishmaniasis
Vitamin deficiency: B12, folate, vitamin E
Metabolic disorders: (mevalonate kinase deficiency)
Rheumatic disease
Autoimmune lymphoproliferative disorder
Mitochondrial deletions (Pearson syndrome)
Inherited BM failure syndrome (Fanconi anemia, dyskeratosis congenita, Shwachman-Diamond syndrome, amegakaryocytic thrombocytopenia, thrombocytopenia with absent radii, radioulnar synostosis (Seckel syndrome)
PNH (rare in childhood)
Acquired aplastic anemia during hematological recovery.

myelodysplasia-related changes in peripheral blood and bone marrow, including myelodysplasia-related cytogenetic abnormalities may also have slowly progressive disease. These cases, considered as refractory anemia with excessive blasts in transformation (RAEB-t) by the French-American-British cooperative classification, may lack the clinical features of acute leukemia and behave more like MDS than AML. They also do not respond to AML-like therapy. Hence, RAEB-t has been retained in childhood MDS as compared to adult MDS where it is no longer retained in the present WHO classification. Follow-up is necessary to monitor the disease in such cases. It is important to note that children having recurrent translocation cytogenetic abnormalities like t(8;21)(q22;q22), inv(16)(p13.1q22) or t(16;16)(p13.1;q22) or t(15;17)(q22;q12) should be considered to have AML regardless of the blast count.

Treatment

The most appropriate therapy for children with RAEB or RAEB-T is unknown. Although most investigators agree that HSCT can improve survival, the importance of cytoreductive therapy prior to grafting remains controversial. Data from the European Working Group of MDS in Childhood (EWOG-MDS) indicate that intensive chemotherapy prior to HSCT will not improve survival. In this study of advanced primary MDS, the probability of survival was about 50% and not influenced by marrow blast percentage at the time of transplantation.

MYELOYDYSPLASIA IN GENETIC DISORDERS

Monosomy 7 is the most common cytogenetic abnormality in childhood MDS and is seen in up to one-third of such cases. Trisomy 8 and trisomy 21 are the second most common chromosomal numerical abnormalities. Presence of a complex karyotype (up to or more than three chromosomal abnormalities including at least one structural aberration) is considered the most important prognostic marker as far as outcome of the cases are concerned.

PRIMARY MDS WITH INCREASED BLASTS

(Refractory Cytopenia with Excess Blasts and Excess Blasts in Transformation; RAEB and RAEB-t)

Refractory Anemia with Excess Blasts (RAEB)

Refractory anemia with excess blasts (RAEB) is characterized by the presence of 2–19% blasts in peripheral blood (PB) or 5–19% blasts in bone marrow (BM). It is further classified as RAEB-1 and RAEB-2 based on the presence of 5–19% blasts in BM/2–4% blasts in PB and 10–19% blasts in BM/5–19% blasts in PB, respectively. There are no data at present to distinguish the prognostic significance of RAEB in children. Children with RAEB generally have stable peripheral blood counts for weeks or months.

Refractory Anemia with Excessive Blasts in Transformation (RAEB-t)

Some cases diagnosed in children with AML with 20–29% blasts in the peripheral blood and/or bone marrow that have

Myeloid Leukemia of Down Syndrome (ML-DS)

Children with trisomy 21 or DS have an approximately 10-20-fold increased risk for developing acute leukemia compared with children without DS. More than half of these cases are AML and this trend persists till about the fourth year of age. Among the myeloid leukemia (ML), the incidence of acute megakaryocytic leukemia (AML M7) from birth till the fourth year of age remains the highest. The incidence of AML M7 is up to 500-fold greater in children with DS till the age of 4 years compared to the general pediatric population. Interestingly, the ratio of acute lymphocytic leukemia (ALL) to AML reverts to that of the general pediatric population once the child completes 5 years of age. Majority of these AML often present with features of MDS and almost uniform presence of *GATA1* mutation. Some neonates with DS or trisomy 21 mosaicism may manifest as transient myeloproliferative disorder (TMD). The cure rate of AML in DS is high. This may be due to an increased in vitro sensitivity of myeloblasts to cytarabine as a result of generation of ara-C triphosphate. Blasts are also sensitive to daunorubicin. The myeloid leukemia seen in young children with DS is unique and classified under the unifying term *myeloid leukemia of DS* (ML-DS).

Transient Myeloproliferative Disorder (TMD)/ Transient Abnormal Myelopoiesis (TAM)/DS Transient Leukemia (DS-TL)

This is an intriguing syndrome which is generally diagnosed in up to 10% of neonates with Down syndrome, usually during the first week of life. TAM cannot be readily distinguished from congenital AML. Blasts in TAM have now been proved to be clonal in origin.

Clinical features of TAM include very elevated leukocyte count with circulating blasts which may be megakaryoblasts as well as erythroblasts, hepatosplenomegaly, and an increased percentage of blasts in the bone marrow. Additional manifestations of DS-TL include cutaneous involvement, hyperviscosity, myelofibrosis, cardiopulmonary failure, splenomegaly, and spleen necrosis.

There is complete clinical and hematological recovery in more than 70% of these neonates within weeks to a maximum of three months of life without therapy. Unfortunately there is a small subgroup of infants with TAM who die from liver failure and multiorgan failure due to megakaryoblastic infiltration of the liver and hepatic fibrosis. Early death in 17% is associated with high WBC at diagnosis, increased bilirubin and liver enzymes and failure to normalize WBC. Almost 30% of infants with TMD/TAM eventually develop AML (mostly AML M7) before 4 years of age. There is usually a prodrome of several months in which there is evidence of persistent thrombocytopenia and BM myelofibrosis

with dysplastic megakaryocytic. Mutations in *GATA-1* gene (an erythroid/megakaryocytic transcription factor) are present in the blast in infants with TMD as well as patients with DS with AML. **Table 3** depicts the differences between TAM and congenital leukemia. Majority of infants with TAM never require therapy in the first month of life; these infants should be observed and given supportive therapy. A small group of infants with liver failure warrants a course of low-dose cytarabine.

JUVENILE MYELOMONOCYTIC LEUKEMIA (JMML)

Juvenile myelomonocytic leukemia is a uniquely pediatric clonal disorder of the hematopoietic stem cell and is the most common form of myeloproliferative syndrome in childhood. It was previously referred to as juvenile chronic monocytic leukemia (JCML) or chronic myelomonocytic leukemia (CMML). The incidence is approximately 1.2 per million, comprising 2-3% of all childhood leukemias but 40% of childhood MDS. Mutations in the *RAS* gene is seen in 20%, in *PTPN11* in 35%, *NF1* gene in 15% and clinical *NF1* in another 15%. **Box 3** depicts diagnostic criteria of JMML.

Differential Diagnosis

Making a diagnosis of JMML is not easy as its clinical and laboratory features can also be associated with other myeloproliferative neoplasms, infection (Epstein-Barr virus, cytomegalovirus, human herpes virus 6, histoplasmosis, mycobacterium and toxoplasmosis), Langerhans cell histiocytosis, hemophagocytic lymphohistiocytosis (HLH), Fanconi anemia, Kostmann syndrome and Down syndrome.

Management

Juvenile myelomonocytic leukemia is a rapidly fatal disorder if left untreated. Intensive chemotherapy is mostly unsuccessful in JMML because of an increased risk of treatment related death, a low rate of true remissions and long-term survival of less than 10%. Allogeneic stem cell transplantation (SCT) is the only curative approach for JMML resulting in long-term survival in more than half the patients. Non SCT treatment includes AML-like therapy, low dose chemotherapy, interferon alpha and 13-cis retinoic acid. Tipifarnib, a farnesyltransferase inhibitor has also been tried. The efficacy of chemotherapy, is however, limited. Low platelet count, age above 2 years, high Hemoglobin F and high bone marrow blast count at diagnosis are the main factors predicting a short survival.

This disorder is described in detail in Section 45 on malignant disorders.

Table 3 Differences between transient abnormal myelopoiesis (TAM) and congenital leukemia

Transient abnormal myelopoiesis	Congenital leukemia
1. Usual subtype is acute megakaryoblastic leukemia	1. Usual subtype are acute monoblastic leukemia and acute megakaryoblastic leukemia
2. Prognosis is excellent and majority recover within 3 months of life	2. Prognosis extremely poor and majority succumb to the disease
3. Majority do not require treatment except close follow-up	3. High dose chemotherapy followed by hematopoietic stem cell transplantation is the only option
4. Always presents in the first week of life	4. Presents at birth or within first month of life
5. Nearly all cases have <i>GATA-1</i> mutations	5. Majority display mixed lineage leukemia (MLL) gene translocation at 11q23
6. Blasts are highly sensitive to chemotherapy, particularly to cytarabine and daunorubicin	6. Blasts are generally resistant to chemotherapy due to MLL gene mutations
7. Commonly presents with hepatosplenomegaly and occasionally cutaneous involvement	7. Twenty five to thirty percent of infants have specific cutaneous infiltrates (leukemia cutis) which usually appear as firm blue or red nodules (Blueberry Muffin)

BOX 3 Diagnostic criteria of juvenile myelomonocytic leukemia (JMML)*Required laboratory criteria (all three required)*

- No Philadelphia chromosome/no *bcr/abl* rearrangement
- Peripheral blood monocyte count $> 1 \times 10^9/L$
- Bone marrow blasts $< 20\%$

Suggestive clinical features

- Hepatomegaly
- Splenomegaly
- Pallor
- Fever
- Skin rash

Additional criteria (minimum of two required)

- Increased HbF (age corrected)
- Myeloid precursors in peripheral blood
- White blood cell count $> 10^9/L$
- Clonal abnormalities, including monosomy 7
- GM-CSF hypersensitivity of myeloid progenitors in vitro.

MORE ON THIS TOPIC

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IN A NUTSHELL

1. Myelodysplastic syndrome in childhood is extremely rare and accounts for less than 5% of all hematopoietic neoplasm in children below the age of 14 years.
2. The primary MDS in children also known as de novo MDS differs from secondary MDS which generally follows congenital or acquired bone marrow (BM) failure syndromes as well as from therapy related MDS commonly resulting from cytotoxic therapy.
3. Many of the morphologic, immunophenotypic and genetic features of MDS in adults are also observed in childhood forms of the disease but there are some significant differences reported, particularly in patients who do not have increased blasts in their peripheral blood (PB) or bone marrow.
4. There are no data at present to distinguish the prognostic significance of Refractory anemia with excess blasts (RAEB-1 and RAEB-2) in children as compared to adults.
5. RAEB-t has been retained in Childhood MDS as compared to Adult MDS where it is no longer retained in the present WHO classification.
6. Monosomy 7 is the most common cytogenetic abnormality in childhood MDS and is seen in up to one-third of such cases.
7. MDS associated with Down syndrome which accounts for approximately one-fourth of cases of childhood MDS is now considered a unique biologic entity synonymous with Down syndrome-related myeloid leukemia and is biologically distinct from other cases of childhood MDS.
8. Refractory cytopenia of childhood (RCC) is the most common type of MDS.
9. The most effective and curative treatment is hematopoietic stem cell transplantation and this is particularly effective in children with monosomy 7 genetic defect as well as those displaying complex karyotype abnormalities provided it is instituted early in the course of the disease.

Section 39 RESPIRATORY DISEASES

Section Editors Varinder Singh, GR Sethi

Chapter 39.1

Anatomy and Physiology of Respiration

Pankaj C Vaidya

The process of respiration in the humans is materialized by both external and internal respiration. *External respiration* includes breathing (moving air in and out of respiratory tract) and ventilation (alveolar air absorption of oxygen and release of carbon dioxide); whereas *internal* or *cellular respiration* involves production of energy by oxidizing substrate molecules.

External respiration takes place in the respiratory tract comprising of upper (starting from the external nares, nasal cavities, nasal septum, paranasal sinuses, pharynx to the larynx) and lower (includes conducting and acinar) airways. The conducting airways (trachea, main bronchi, segmental bronchi, subsegmental bronchi (up to 5th generation), smaller bronchi (about 15 generations), bronchioles and terminal bronchioles) are connected by the transitional bronchioles with the acinar airways [respiratory bronchioles (3 generations), alveolar ducts and alveolar sacs] (Fig. 1).

EMBRYOLOGY OF THE LUNGS

The phases of development of the human lungs are shown in **Figure 2**. Postnatally, alveoli continue to develop till 5–8 years and enlarge through adolescence. The number of alveoli and alveolar surface area at birth (in a term neonate) are 20–50 million and 2.8 m² respectively, which increase at 8 years to 300 million and 32 m² respectively. In adulthood the alveolar surface area increases to 75 m².

ANATOMY OF LUNGS

Blood Supply of the Lungs

Bronchial arteries, derived from the thoracic aorta or upper aortic intercostal arteries, supply blood for the nutrition of the lungs. Blood supply to the conducting airways is from the bronchial vessels and to the terminal respiratory units from the pulmonary vessels. Pulmonary veins are formed from the capillary network and join together to form the four main pulmonary veins, which drain oxygenated blood to the right atrium. Pulmonary artery pressure is high at birth and falls over the next days and weeks, in response to the higher oxygen levels. Bronchial arterial circulation is at systemic pressure.

Lymphatics of the Lung

The pulmonary lymphatics comprise of lymph ducts, lymph nodes and thoracic duct and there are two networks: pleural and parenchymal. These are vital for the removal of lung liquid at birth.

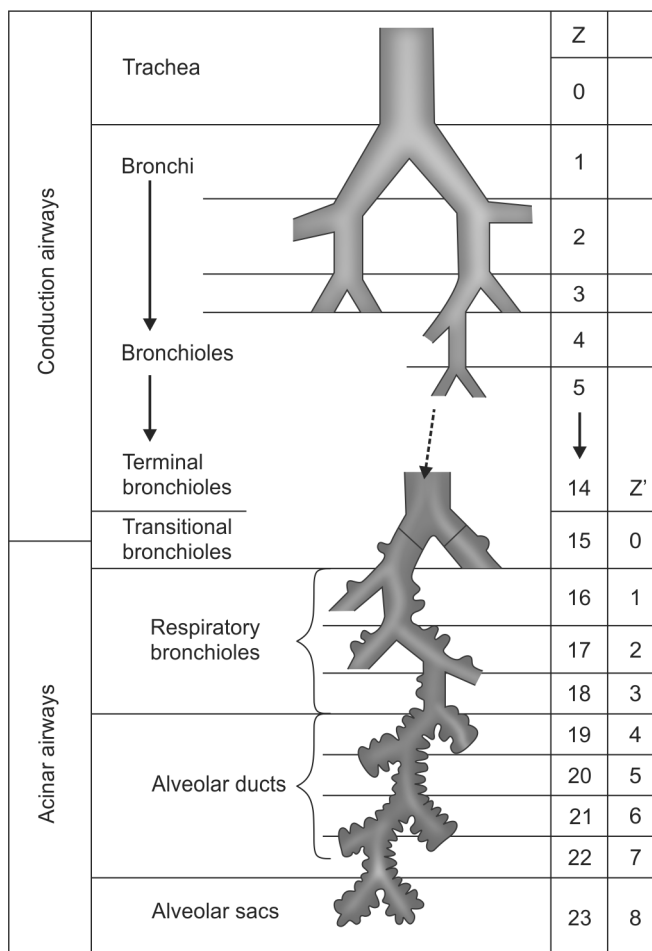


Figure 1 Human lung's airway branching

Owing to valves, the flow in the lymph channels moves in one direction and most drainage is toward the hilum. On the left side, veins follow the trachea and empty into the thoracic duct which drains into the veins on the left side of the neck while on the right side the main lymphatic ducts follow the right side of the trachea and join the venous system at the right jugular and subclavian veins junction. Lymphatic drainage of the lung is complex and varies from individual to individual.

Nerve Supply of the Lung

It is from the branches of the thoracic sympathetic ganglia and the vagus nerve. Lungs are supplied by the upper 3–5 sympathetic ganglia branches while the lower supply intercostal nerves. The sensory (afferent) system is mainly in the vagus nerve and the motor (efferent) pathways are shown in **Figure 3**.

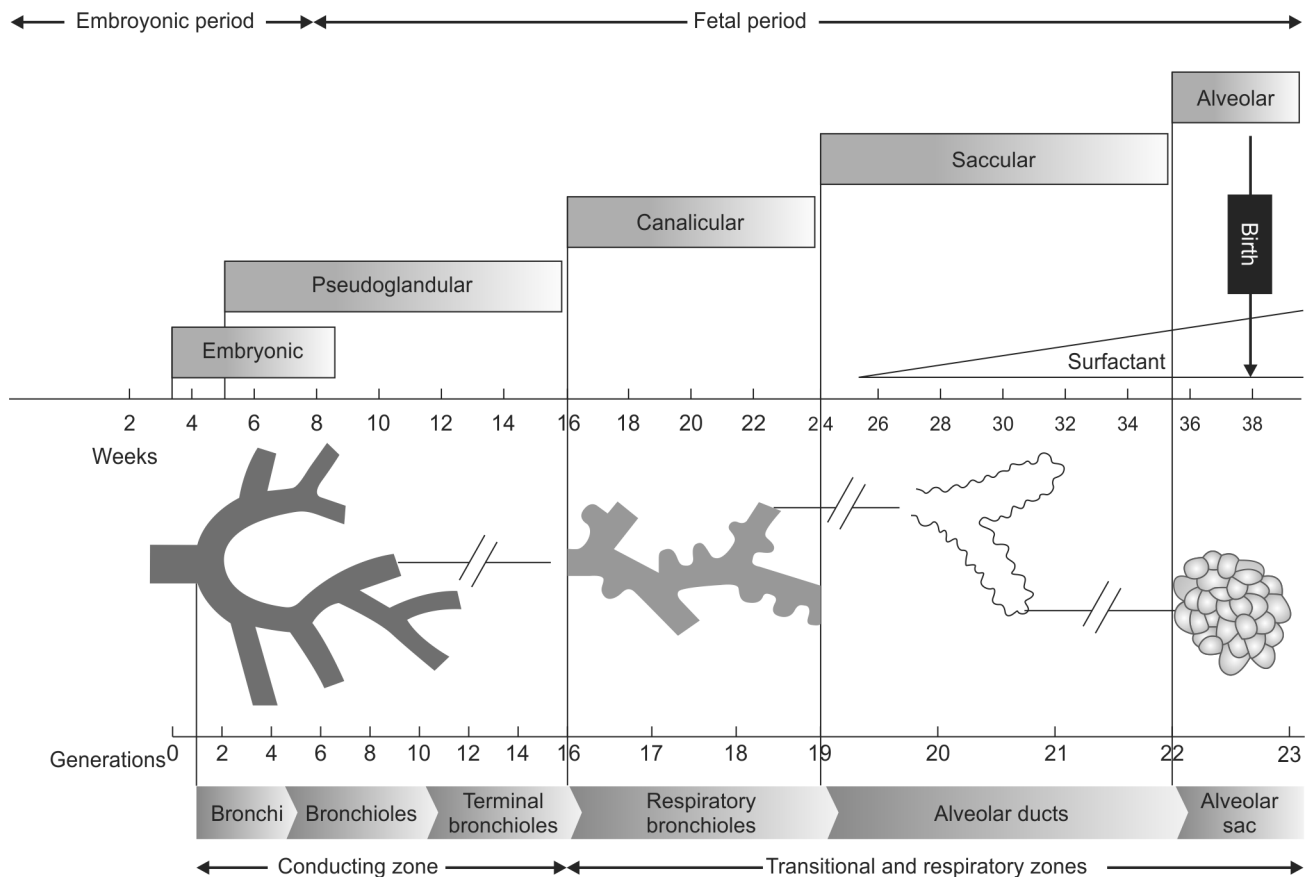


Figure 2 The five phases of embryonic development (approximate and overlapping)

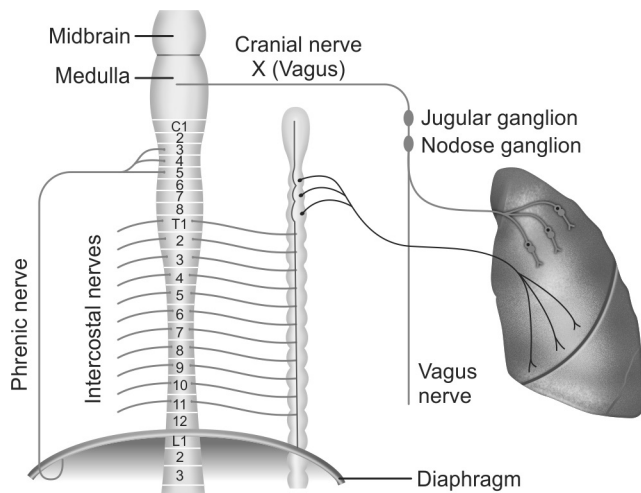


Figure 3 Efferent nervous system of the lung

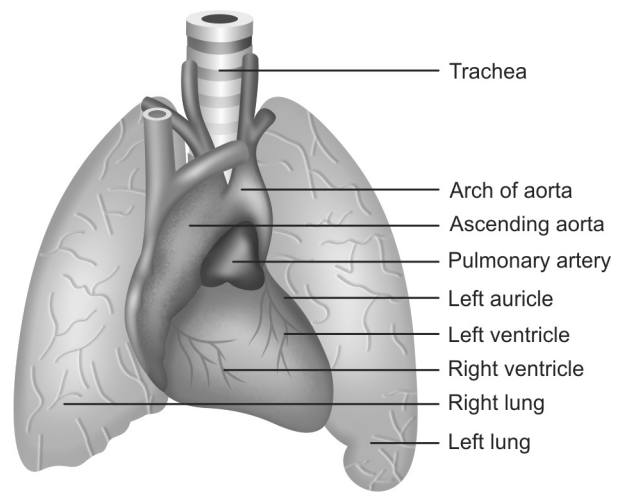


Figure 4 Lungs and heart in the thorax, front view (retracted anterior borders of the lungs)

The Lungs

Both lungs occupy the thoracic cavity, separated by the heart and mediastinum (**Figs 4 and 5**). They are spongy and pink in early years and with age gradually become grayer. The apex extends into the root of the neck and the base which is concave rests on the convexity of the diaphragm. The right lung has three lobes and two fissures and the left has two lobes and one fissure. Each lung gets divided functionally into 10 subdivisions because of branching

of the bronchial tree known as the bronchopulmonary segments (**Figs 6 and 7**). Each segment has an autonomous blood supply and airflow.

Lungs are covered by both visceral/pulmonary (extends into the fissures) and parietal (lines the inner surface of the thoracic cavity) pleurae, which join at the root of the lung (hilum) with an expandable space between the two layers.

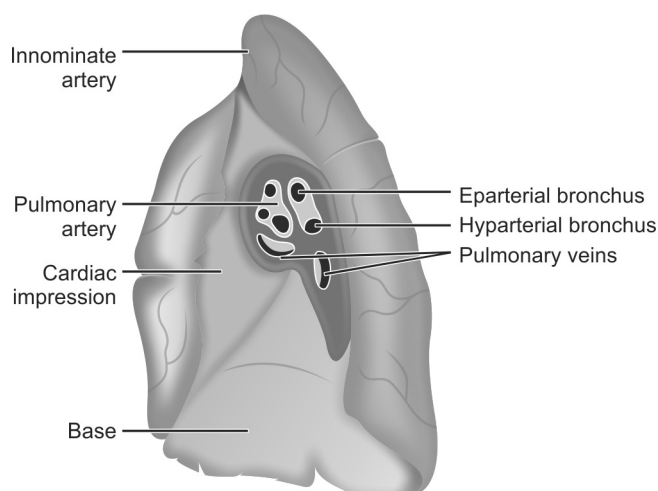


Figure 5 Right lung (mediastinal surface)

Mediastinum

It lies in the thoracic cavity between the plurae of the two lungs bounded anteriorly by the sternum and posteriorly by the vertebral column. The superior mediastinum is above the pericardium (contains thymus, trachea, esophagus, thoracic duct, and the upper great vessels including the arch of the aorta), while below the pericardium there are three parts—anterior mediastinum which lies in front of the pericardium, middle mediastinum which contains the heart and pericardium and posterior mediastinum which is behind the heart (**Fig. 4**). The hila of the lungs are where the structures of the lung enter from the mediastinum, the usual level being anteriorly the third-fourth costal cartilage and posteriorly the fifth-seventh thoracic vertebrae.

Muscles of Respiration

These are the intercostal muscles and diaphragm. The right diaphragm overlying the liver is higher than the left, which overlies the stomach and spleen. There are three major openings—at

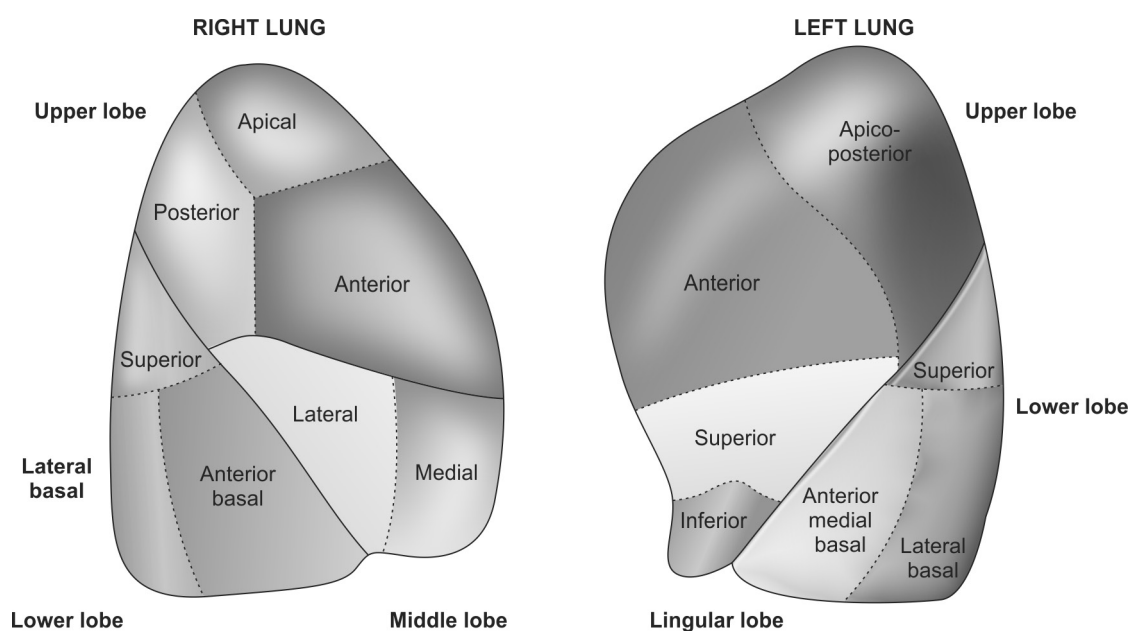
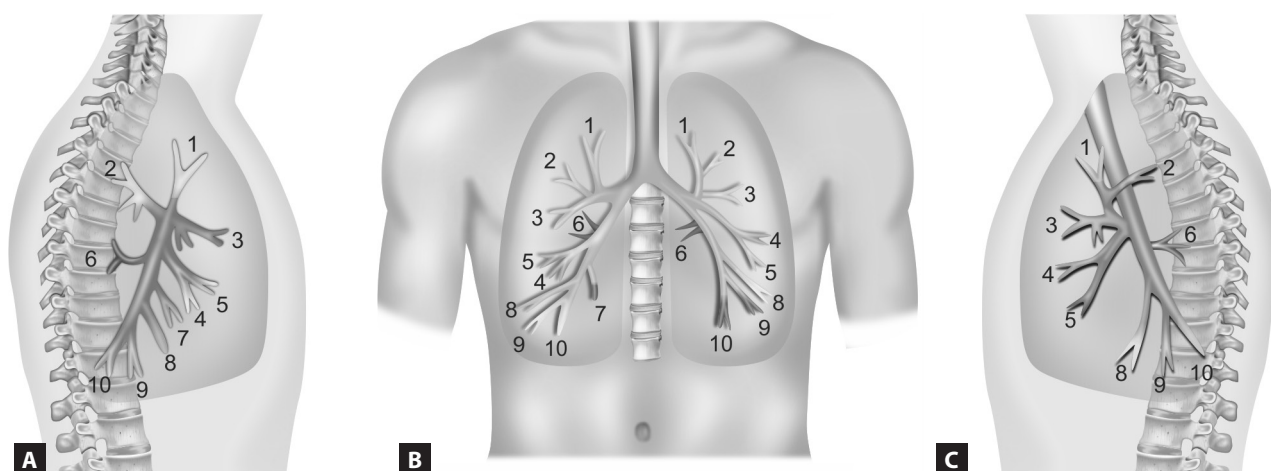


Figure 6 The bronchopulmonary segments



Figures 7A to C The nomenclature of bronchopulmonary anatomy. (A) Right lateral view; (B) Anterior view; (C) Left lateral view. Segments: Right upper lobe: (1) apical, (2) posterior, (3) anterior. Right middle lobe: (4) lateral, (5) medial. Right lower lobe: (6) superior (apical), (7) medial basal, (8) anterior basal, (9) lateral basal, (10) posterior basal. Left upper lobe: (1) apical, (2) posterior, (3) anterior, (4) superior lingual, (5) inferior lingual. Left lower lobe: (6) superior (apical), (7) medial basal, (8) anterior basal, (9) lateral basal, (10) posterior basal. Note absence of medial basal segment (7) in the left lung

the thoracic vertebral level (T12) is inferior vena cava, at T10 is esophagus, and at T12 is aorta. The opening of anterior diaphragm is the foramen of Morgagni and of the posterior is the foramen of Bochdalek, which are sites of diaphragmatic hernia (**Fig. 8**).

The diaphragm is attached to the lower costal margins and the leaves are dome shaped. With inspiration, the diaphragm flattens and the lower border of the lung correspondingly descends resulting in a different level of lower lung border.

PULMONARY PHYSIOLOGY

The respiratory system's function is to provide oxygen to arterial blood to nourish the body's tissues and to remove carbon dioxide from the returning venous blood. Gas exchange takes place at the level of the alveoli surrounded by a network of thin capillaries. Oxygen and carbon dioxide move between the air and blood by a process of diffusion. Air is brought to the alveoli by branching bronchi and bronchioles. The muscles of respiration act as pump to move air in and out of the lungs. Elastic properties of the lung and chest wall and airway resistance affect the work and efficiency of the system. Disease processes that alter these relationships can lead to respiratory failure that is defined as failure of the lungs to oxygenate and ventilate adequately.

Gas Exchange

Partial pressure of gases in atmosphere and the lung are shown in **Table 1**. Dry atmospheric air (primarily nitrogen, 20.93% oxygen and minimal carbon dioxide) gets humidified while traveling down the airways into the lungs. The alveolar PO_2 depends on the balance between the amount that flows in and the amount that is removed by the pulmonary capillaries. It decreases in the absence of fresh air supply (atelectasis), elevation of PCO_2 (hypoventilation) or at low barometric pressure (high altitude).

Gas exchange occurs on a large surface area when gas moves in and out of the alveolus and blood flows through the pulmonary capillary vessels. As shown in **Figure 9** the driving force for gas

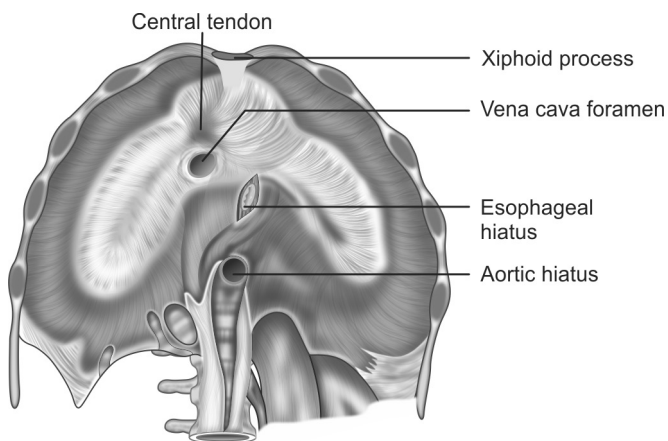


Figure 8 Diaphragm image from below

Table 1 Partial pressure of gases in atmosphere and the lung

	Air (mm Hg)	Humidified air (mm Hg)	Alveoli (mm Hg)
Oxygen	159	149	104
Carbon dioxide	0.3	0.3	40
Nitrogen	600.6	564	569
Water vapor	0	47	47

exchange is the pressure difference of PO_2 and PCO_2 between the venous blood and alveoli. Normally, the gases equilibrate fully and thus the PO_2 and PCO_2 of pulmonary capillary blood equals that of the alveoli.

O_2 consumption and CO_2 production In 1 minute the total amount of O_2 taken up by the body is O_2 consumption (VO_2) and amount of CO_2 produced is CO_2 production (VCO_2). Both are increased with exercise. The ratio between the two is respiratory quotient and is usually 0.8.

Ventilation

It is the process of bringing air in and out of the lungs. During inspiration, the size of the thoracic cavity increases and air moves into the lungs. It is carried through the conducting airways to the alveoli, which are responsible for gas exchange. Relationship of tidal volume to dead space and alveolar volume is depicted in **Figure 10**. Components of total ventilation are shown in **Figure 11**.

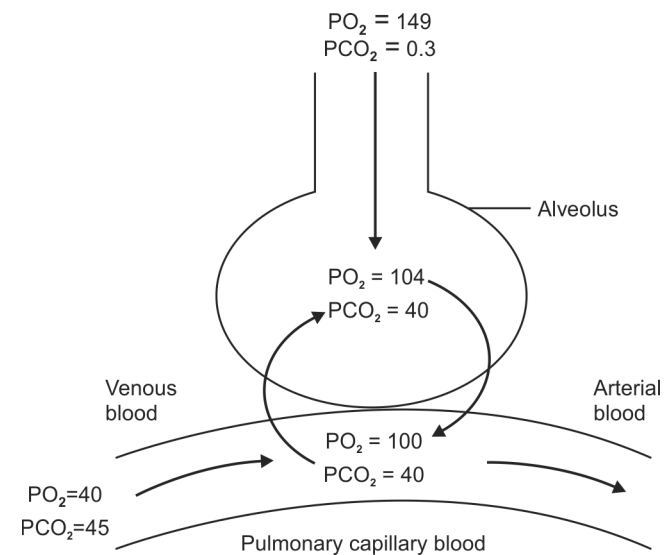


Figure 9 Gas exchange in the alveolus

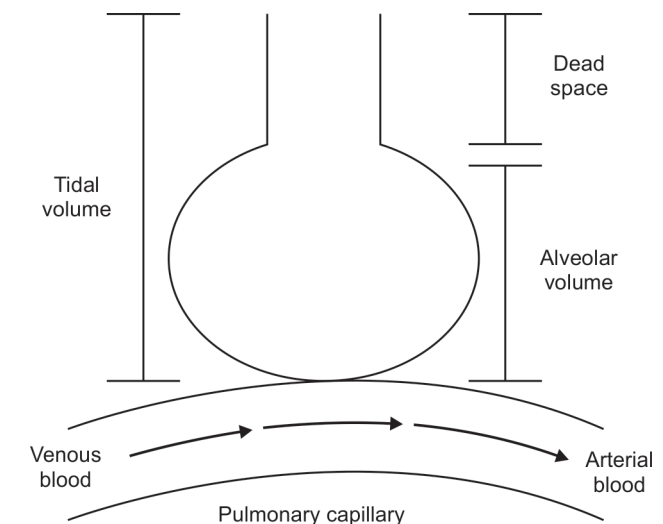


Figure 10 Relationship of tidal volume to dead space and alveolar volume. With each breath (tidal volume) some air goes into the alveoli and is available for gas exchange (alveolar volume)

Relationship of ventilation to arterial PCO_2 (Fig. 12) Decrease in tidal volume and respiratory rate decrease the total ventilation and increase the arterial carbon dioxide tension. Increase in respiratory rate and tidal volume increase the total ventilation and decrease the arterial carbon dioxide tension. Dead space changes affect carbon dioxide levels and alveolar ventilation but do not affect total ventilation (Table 2).

Regulation of arterial PCO_2 The arterial carbon dioxide concentration reflects a balance between carbon dioxide production and elimination. More carbon dioxide is produced

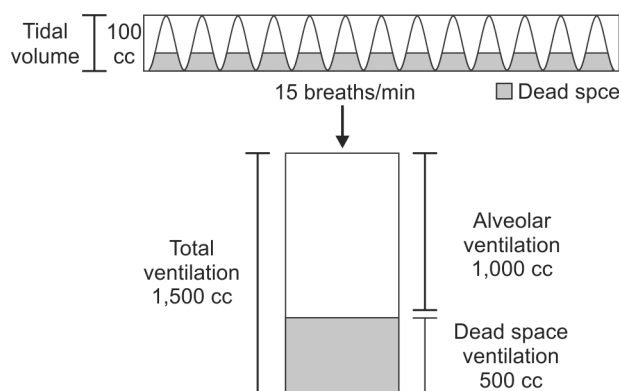


Figure 11 Components of total ventilation: tidal volume, respiratory rate, alveolar ventilation and dead space ventilation. An example showing number of breaths per minute multiplied by the volume of each breath is total ventilation

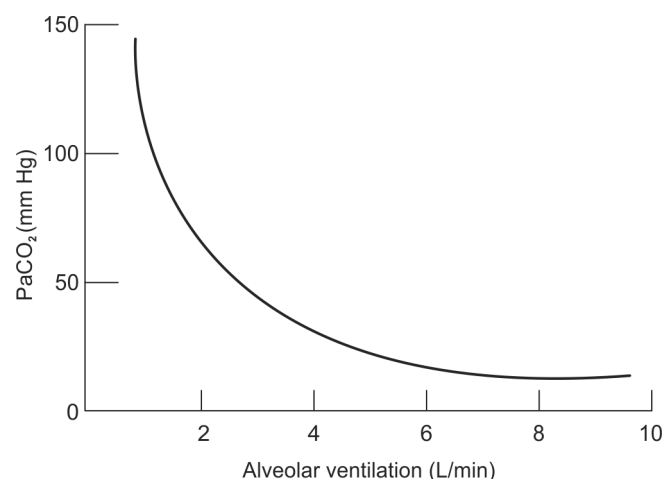


Figure 12 Relationship between ventilation and carbon dioxide levels in the lung

when the metabolic rate is increased. Ventilation is controlled by sensors called chemoreceptors (brain and carotid bodies) which sense changes in arterial carbon dioxide concentration and respond by activating effectors that alter ventilation to keep arterial carbon dioxide concentration normal.

Acid-Base Status

In the blood, carbon dioxide gets transported in three forms: dissolved, bicarbonate, and combined with proteins such as carbamino compounds. Ninety percent of it is carried as bicarbonate in arterial blood. In the red blood cell water and carbon dioxide are converted to carbonic acid (in the presence of the enzyme carbonic anhydrase) which spontaneously dissociates into bicarbonate and hydrogen ions (acid).

The blood pH depends on the relationship between carbon dioxide and bicarbonate. As the arterial PCO_2 increases, the pH decreases, known as respiratory acidosis and as the arterial PCO_2 decreases, the pH increases, known as respiratory alkalosis. The concentration of carbon dioxide is regulated by the lungs and that of bicarbonate controlled by the kidneys. In response to a respiratory acidosis, the kidneys compensate over 3–5 days by conserving bicarbonate and create secondary metabolic acidosis. While in response to a respiratory alkalosis the kidneys eliminate excess bicarbonate and create a secondary metabolic acidosis in compensation (Table 3).

The primary acid-base disorders and the compensations can be determined by plotting the values on a nomogram (Fig. 13). For acute respiratory acidosis an increase in PCO_2 of 10 mm Hg will decrease the pH by 0.08 and the bicarbonate by 1 mEq/L. In chronic respiratory acidosis, after renal compensation, the bicarbonate will increase by a total of 4 mEq/L for each 10 mm rise in PCO_2 . In acute and chronic respiratory alkalosis, similar changes occur in the opposite direction. Remembering the relationship between change in PCO_2 and pH can be useful in determining whether a patient has a compensated, partially compensated, or uncompensated respiratory acidosis.

Oxygenation

Oxygen reaches the alveoli through the conducting airways and diffuses across the very thin membrane to the capillary blood. Normally, oxygen composes 21% of air. The amount of oxygen in the alveolus is determined by the presence of other gases, fresh air supply and barometric pressure changes. The PO_2 decreases when the PCO_2 increases. The PO_2 depends on a fresh flow of air, so when the airflow decreases like in apnea, atelectasis or mucous plugging, then the PO_2 in the alveolus decreases. It also depends on the atmospheric pressure, which is low at high altitude resulting into less oxygen availability causing hypoxemia or low arterial oxygen level.

In the red blood cell, oxygen is primarily bound to hemoglobin and a small amount is dissolved in plasma. Normally, a red

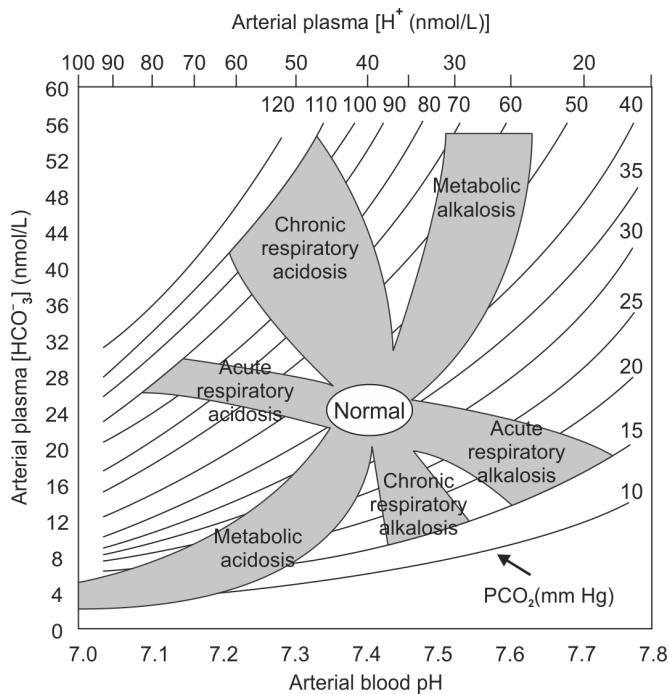
Table 2 Effect of respiratory rate, tidal volume and dead space on total ventilation and arterial carbon dioxide level

Respiratory rate (breaths/minute)	Tidal volume	Dead space	Total ventilation	Arterial PCO_2	Causes
↓	↔	↔	↓	↑	Medications, alcohol, central nervous system infections, seizures, apnea
↔	↓	↔	↓	↑	Chest wall trauma, neuromuscular weakness, lung disease
↔	↔	↑	↔	↑	Acute respiratory distress syndrome, scoliosis, pulmonary embolus
↑	↔	↔	↑	↓	Metabolic acidosis, salicylate overdose, anxiety, pain
↔	↑	↔	↑	↓	Metabolic acidosis, salicylate overdose, anxiety, pain
↔	↔	↓	↔	↓	Mechanical ventilation, deep breathing

Table 3 Primary acid-base disorders and compensations

	Carbon dioxide	pH	Bicarbonate
Acute respiratory acidosis	↑	↓	↑
Chronic respiratory acidosis	↑	↓	↑
Acute respiratory alkalosis	↓	↑	↓
Chronic respiratory alkalosis	↓	↑	↓
Metabolic acidosis	↓	↓	↓
Metabolic alkalosis	↑	↑	↑

(Note: Bold arrows indicate the primary event)

**Figure 13** Acid-base abnormalities nomogram

blood cell takes about three-fourths of a second to transverse the pulmonary capillary bed and about one-fourth of a second for the oxygen to be fully transferred to the red blood cell. The transfer may take longer and unable to get completed by the end of its transit time if the capillary membrane gets thickened. It can be aggravated by exercise, as the blood may not have adequate time to get saturated as it moves more quickly through the lungs.

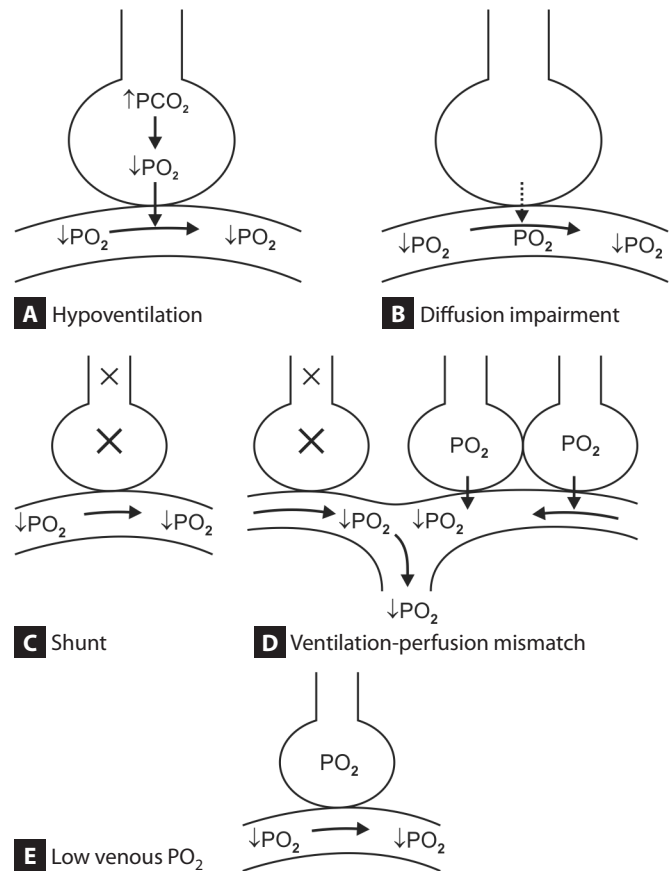
MECHANISMS OF HYPOXEMIA

The primary processes contributing to hypoxemia (abnormally low arterial blood oxygen) are shown in **Figures 14A to E**.

Oxygen Transport

Oxygen is primarily carried in the blood bound to hemoglobin and a small amount is dissolved in the plasma. The total amount carried by the blood is known as *oxygen content* and the maximum amount of oxygen that can be combined with hemoglobin is called *oxygen capacity*. One gram of hemoglobin can combine with 1.34 mL of oxygen.

The *oxygen saturation* is the percentage of binding sites of hemoglobin that have oxygen attached. The normal oxygen saturation is 98% for arterial blood and 75% for venous blood.



Figures 14A to E Causes of hypoxemia. (A) Hypoventilation: ventilation is decreased and there is an increase in PCO_2 resulting in decrease of alveolar PO_2 ; (B) Diffusion impairment: diffusion across the alveolar-capillary membrane to the hemoglobin in the red blood cell is decreased; (C) Shunt: pulmonary venous blood bypasses the lung without being oxygenated example: right-to-left shunt in congenital cardiac disease or arteriovenous malformation; (D) Ventilation/perfusion mismatch: some areas of the lung are nonfunctional and poorly oxygenate the venous blood. There is mixing of blood from functioning alveolar units; (E) Low venous PO_2 : the PO_2 in the venous blood may be abnormally low because of anemia, fever or decreased cardiac output. In the presence of lung disease, shunt or exercise, it may not be fully oxygenated as it completes its course through the lung

In general, oxygen saturation increases as the PO_2 of the blood increases. The dissociation curve for oxygen is "S" shaped (**Fig. 15**). Between an oxygen tension of 20 mm Hg and 75 mm Hg, there is a sharp, linear rise in oxygen saturation.

Factors altering affinity of hemoglobin from oxygen As shown in **Figure 16**, many factors shift the oxygen dissociation curve to the right and cause oxygen to bind less avidly to hemoglobin (increased temperature, acidosis, hypercarbia and increased 2, 3 diphosphoglycerate). Conversely, decreased temperature, alkalosis and low CO_2 levels shift the curve to the left resulting in O_2 binding more avidly to the hemoglobin which leads to lesser delivery to tissues.

Assessment of Oxygenation and Ventilation

It is extremely difficult to assess the adequacy of oxygenation and ventilation by physical examination. The most specific sign of impaired oxygenation, i.e. cyanosis, can be detected usually at an oxyhemoglobin saturation of 80%. Arterial oxygen saturation can

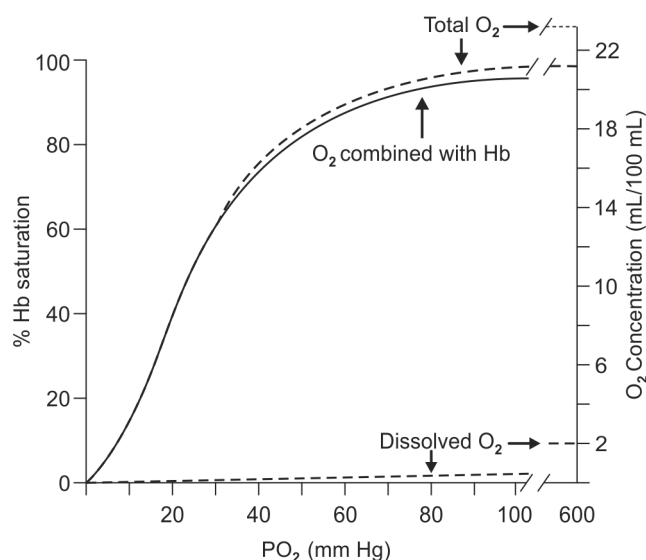


Figure 15 Oxygen dissociation curve (for pH 7.4, PCO_2 40 mm Hg, 37°C and hemoglobin concentration 15 g/100 mL)

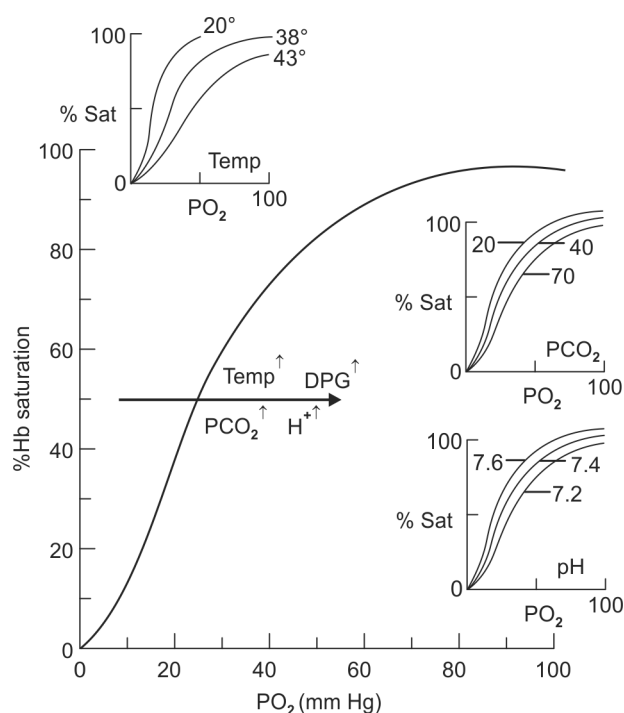


Figure 16 Factors that change the oxygen dissociation curve

Table 4 Measures of oxygenation impairment

Oxygen	Normal values (mm Hg)
$PAO_2 - PaO_2$	< 10
PaO_2 / PAO_2	1
PaO_2 / FiO_2	500

be assessed noninvasively using pulse oximetry. Arterial PCO_2 can be assessed noninvasively by end-tidal CO_2 monitoring. Arterial blood gas analysis is the gold standard for assessing PO_2 and PCO_2 . The degree of impairment of oxygenation can be assessed by calculating the A-a gradient (**Table 4**).

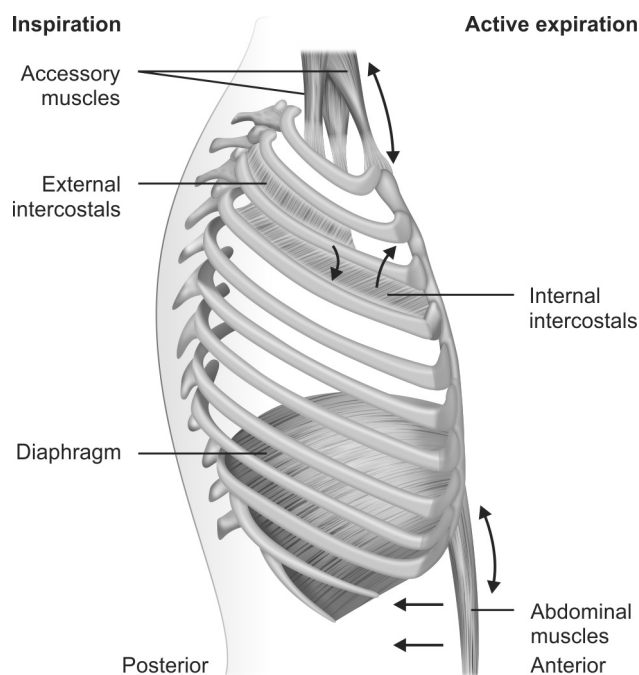


Figure 17 Muscles of breathing

MECHANICS OF BREATHING

The muscles of respiration act like a pump to move air in and out of the lungs. The efficiency of the pump is determined by the elastic properties of the chest wall and lungs and the resistance of the airways. Disease processes can alter these relationships and lead to respiratory failure.

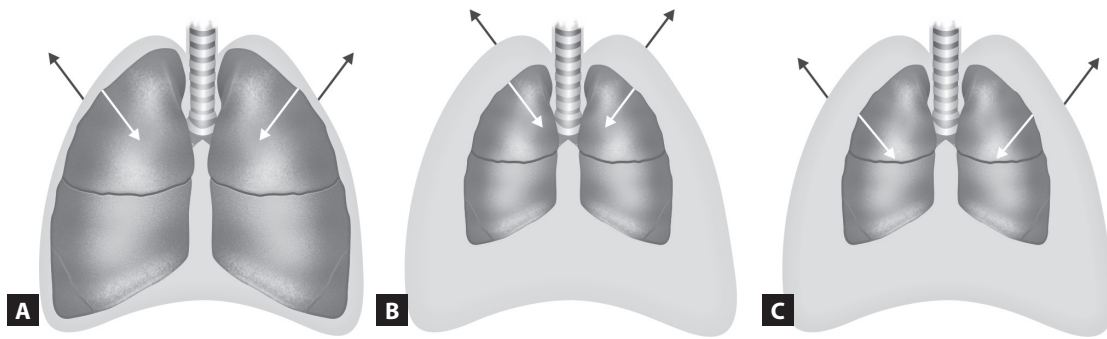
Muscles of breathing The inspiratory muscles are the diaphragm, external intercostals and accessory muscles such as the sternocleidomastoid and scalene. Expiration with quiet breathing is passive. Active expiration requires the use of the abdominal and internal intercostal muscles (**Fig. 17**).

Elastic properties of the lung and chest wall The ease with which the lungs can be stretched is compliance; it gets reduced in fibrosis, pulmonary edema or acute respiratory distress syndrome while it increases in emphysema with aging. The resting lung volume (functional residual capacity) represents the balance between the tendency of the lungs to collapse and the chest wall to recoil (**Figs 18A to C**).

Airway resistance It is the force that opposes the forward motion of the airflow. About 25–40% of the total airway resistance is located in the upper airway. In laminar airflow, resistance is directly proportional to the radius of the airways. Therefore, if the radius of an airway is narrowed by half, the resistance increases by 16-fold. In the airways of infants and children which are already narrow relative to an adult, small change in the airway caliber produce large changes in resistance.

Work of breathing It is proportional to the tidal volume and the change in pressure that is required to move the air. It increases when the compliance of chest wall or lung is decreased or airway resistance is increased. Infants and young children are at higher risk of respiratory failure because their chest walls are more compliant and their diaphragms are flatter and more prone to fatigue.

Assessment of lung mechanics Measurements of airflow, lung volumes and airway resistance can be done by pulmonary function testing.



Figures 18A to C Interactions of the chest wall and lung in diseased states. (A) In the normal lung, the outward recoil of the chest wall balances the inward recoil of the lung. The final volume of the lung depends on the equilibrium between the two; (B) If the chest wall becomes less compliant and stiffer; there is less outward force to balance out the inward recoil of the lungs. The result is a smaller lung volume. Examples: obesity, neuromuscular weakness, trauma to or defects in the chest wall; (C) If the lungs become less compliant, they overcome the outward force of the chest wall and have a smaller resting volume. Examples: pulmonary edema, interstitial fibrosis, acute respiratory distress syndrome

IN A NUTSHELL

1. Human respiration is materialized by both external (breathing and ventilation) and internal/cellular respiration.
2. The right lung has three lobes and two fissures and the left has two lobes and one fissure. Each lung has 10 bronchopulmonary segments.
3. Bronchial arteries nourish the lungs while pleural and pulmonary lymphatics drain the lungs. Muscles of respiration are the intercostal muscles and diaphragm.
4. Gas exchange occurs on a large surface area when gas moves in and out of the alveolus and blood flows through the pulmonary capillary vessels. The blood pH depends on the relationship between carbon dioxide and bicarbonate.
5. For acute respiratory acidosis, an increase in PCO_2 of 10 mm Hg will decrease the pH by 0.08 and the bicarbonate by 1 mEq/L. In chronic respiratory acidosis, after renal compensation, the bicarbonate will increase by a total of 4 mEq/L for each 10 mm rise in PCO_2 . In acute and chronic respiratory alkalosis, similar changes occur in the opposite direction.
6. The amount of oxygen in the alveolus is determined by the presence of other gases, fresh air supply and barometric pressure changes. The primary processes contributing to hypoxemia (abnormally low arterial blood oxygen) are hypoventilation, diffusion impairment, shunt, ventilation/perfusion mismatch and low venous PO_2 .
7. Oxygen is primarily carried in the blood bound to hemoglobin and a small amount is dissolved in the plasma.

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Chapter 39.2

Approach to Diagnosis of a Respiratory Disorder

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Respiratory disorders are the most common causes of morbidity and mortality among children of all ages. The presentation may vary from trivial to life-threatening symptoms. While a carefully conducted history and physical examination are vital for a correct diagnosis, various laboratory and radiological investigations aid in finally clinching the diagnosis. Disorders involving other organ systems may also present with symptoms related to respiratory system.

HISTORY

The evaluation of a child with respiratory disorder should start with the history of present illness, past history, family history as well as antenatal and birth history. The parents should be inquired regarding the chief complaint for presentation at hospital, along with the frequency, total duration, severity and onset of symptom. History of prior treatment and response to it should be recorded. History of past illness will include all previous respiratory and other complaints. These include history suggestive of recurrent lower respiratory tract infections (seen in structural disorders of lower and upper airway, cystic fibrosis, immotile cilia syndrome, primary immunodeficiency disorders, HIV), known allergy and malnutrition. The family/environmental history will provide information about history of contact or that suggestive of asthma in relatives, nutritional and financial status of the family, and history of exposure to allergens. The detailed history-taking of the cardinal respiratory complaints is discussed here:

Cough

A complete evaluation of cough requires detailed history on following points: *Nature of cough*—whether dry or wet and if wet—the *color of the sputum*/whether blood tinged or not; *Diurnal variation*: At what time of the day or night does it occur; *Aggravating or relieving factors*; any *association with feeding* (increase in cough and choking episodes while feeding may indicate gastroesophageal reflux disease or H-type tracheoesophageal fistula or swallowing dysfunction) or exercise (asthma). The *character of the cough* also helps, e.g., cough due to postnasal drip in a child having sinusitis can be dry, throat-clearing type while a loud honking cough occurring only during the day time when the child is conscious of the surroundings in the presence of normal respiratory examination suggests psychogenic cough.

Chest Pain

A *catching* pain on deep inspiration may indicate underlying pleural effusion. Chest pain aggravated by coughing/sneezing may suggest underlying pleural disease or rib fracture. Chest pain too localized or very vaguely placed may not be due to any serious illness particularly if there are no other accompanying symptoms.

Difficulty in Breathing

Difficulty in breathing is usually preceded by a prodrome of fever, cough or coryza, in which case it could be due to underlying lower respiratory tract infection like bronchiolitis, pneumonia or wheeze associated lower respiratory tract infection (WALRI). It is important to ask whether the onset was sudden or gradual and how rapid was the progression. Sudden onset difficulty in breathing

following an episode of choking indicates foreign body aspiration. If breathlessness is sudden and is associated with sharp pain in the chest with very rapid progression it might suggest a pneumothorax or pleural effusion. Gradual onset of dyspnea with previous history of increasing pallor or bleeding diathesis indicates congestive cardiac failure. In a child with previous history of repeated episodes of hospitalization since early infancy in view of pneumonia, and history of suck-rest-suck cycle during feeding, there could be underlying congenital acyanotic heart disease with increased pulmonary blood flow. Hyperventilation in isolation (without other signs and symptoms of respiratory disorder) might be psychogenic especially in adolescent children or it may be provoked by fever. However, if it is associated with history of poor growth or delayed mental development/convulsions, it might suggest metabolic acidosis with respiratory compensation due to an underlying renal problem or inborn error of metabolism. In a patient with history of fever, convulsions and alteration in sensorium, hyperventilation is indicative of raised intracranial tension.

Other Complaints

Following are other important clinical pointers specific to some common conditions, as obtainable in the history:

- Gastroesophageal reflux disease, swallowing disorders, children with history of surgery in upper aerodigestive tract are at increased risk of recurrent pneumonia.
- *Atopy*: History of infantile eczema, hay fever, allergic dermatitis in child or parental history of asthma or skin allergies may be an important feature in children with allergic rhinitis or bronchial asthma.
- Growth failure, recurrent skin and other infections, history of blood transfusion in child or injection drug abuse in parents may provide a valuable clinical clue toward primary immunodeficiency disorders or HIV infection.
- *Environmental injury*: Exposure to dust due to construction in the house/neighborhood, presence of pet animals or birds, exposure to environmental pollutants and smoke from passive smoking, automobiles and household sources.
- History of close contact with a case of tuberculosis.
- *Associated symptoms*: Presence of associated symptoms may help in localization of respiratory disorder. Pedal edema, feeding problems, dyspnea, and exercise intolerance indicates congestive heart failure and may be due to underlying pulmonary artery hypertension because of chronic lung disease or chronic upper airway obstruction or due to a primary cardiac disease. Infections of paranasal sinuses may be associated with headache and frontal tenderness. Snoring is commonly seen in children with chronic adenotonsillar enlargement. Presence of malabsorption should prompt investigation for cystic fibrosis. History of recurrent blepharoconjunctivitis suggests predisposition to allergic airway disease. Development delay or other chronic neurological diseases are associated with aspiration and hence recurrent respiratory infections.

PHYSICAL EXAMINATION

A thorough general physical examination is extremely important in the approach to a child with respiratory disorder. The respiratory rate should be counted for one full minute making sure that the child is not crying. The respiratory rate is an important indicator of respiratory illness and should be examined at rest or in sleeping state. However, high grade fever, psychiatric illness and metabolic acidosis due to other cause may be associated with tachypnea even in absence of respiratory illness.

Nasal flaring and use of accessory muscles of respiration (sternocleidomastoid) are indicators of respiratory distress. Both are adaptive mechanisms with nasal flaring reducing the nasal

resistance to flow of air and use of accessory muscles helps to increase the respiratory effort. Respiratory distress may also be seen in children with neuromuscular disorders. The respiratory pattern and depth may also point toward a particular pathology. Shallow and rapid respiration is seen in children with restrictive lung disease. Deep and rapid respiratory efforts may be indicative of metabolic acidosis and hypoxia rather than true respiratory disease. On contrary, the shallow and slow breaths may be seen in metabolic alkalosis as a result of compensatory retention of CO_2 . Hyperpnea alternating with apnea (Biot respiration) is associated with brain stem lesion involving centers for respiratory control. Cheyne-Stokes respiratory pattern is characterized by gradually increasing and decreasing respirations and is seen in comatose patients.

Recording the anthropometry is as important as is looking for presence of cyanosis, pallor and clubbing. Supraclavicular and cervical lymph nodes should form part of the examination routinely.

Upper Airway

An examination of the upper airway will indicate presence of nasal foreign body or infection, tonsillar enlargement, or presence of stridor. The tracheal position should be confirmed during clinical examination of neck. The deviation of trachea may be seen due to a mass in neck or disorders related to lung. The trachea may shift away from abnormal lung (pneumothorax, pleural effusion, congenital lobar emphysema, inhaled foreign body) or toward the abnormal lung (lung collapse, ipsilateral lung agenesis or hypoplasia).

Chest

Inspection The shape of chest and presence of any chest wall deformity should be carefully inspected. A barrel chest (increased anteroposterior dimension) denotes obstructive lung disease. *Pectus excavatum* also termed as *funnel chest* and *pectus carinatum* also termed as pigeon's chest can be seen as a result of persistently increased work of breathing as seen in chronic asthma, cystic fibrosis or lung fibrosis.

Use of accessory muscles of respiration may indicate severity of respiratory distress and intercostal recession may point toward airway obstruction and a noncompliant lung. The symmetry of chest movement and presence of retractions should be noted.

The relative duration of inspiratory and expiratory phase may also vary with respiratory illness. The expiratory and inspiratory phases of respiration are roughly of equal duration in children. A prolonged expiratory phase may be seen in diseases associated with significant bronchospasm (e.g., bronchial asthma, acute bronchiolitis). Younger children normally may have some abdominal breathing; however, conspicuous abdominal breathing may be a feature of diaphragmatic and other respiratory muscle weakness.

Palpation The chest should be palpated with the palm and fingertips of the palpating hand. The abnormal palpatory findings include friction rubs, which are usually felt in sync with the respiratory pattern. Vibrations in association with voice (tactile fremitus) may also be palpated in the intercostal spaces and is decreased in the presence of major airway obstruction (atelectasis), pleural fluid, or pleural thickening. Chest expansion should be measured by both hands anteroposteriorly holding the child's chest wall and comparing any asymmetry of movement of either hand. Any shift of point of maximum cardiac impulse should be noted; it may shift contralaterally with effusion/pneumothorax and ipsilaterally with volume loss/atelectasis.

Percussion Percussion should be performed with the child sitting straight with the head neutral, and using the indirect method (one finger strikes on the middle finger of the other hand placed on an interspace). A gentle force should be used so as to avoid causing

injury, especially in a young child). Percussion of the chest may elicit the following sounds:

- **Tympany:** Normally heard with percussion of the abdomen, is heard in the chest with a pneumothorax.
- **Resonance:** Resonance is the normal sound heard on percussion of a normal chest.
- **Hyper-resonance:** Accentuation of the normal percussion occurs with states of hyperinflation like emphysema or asthma.
- **Impaired or flat:** A flat sound on percussion comes out on percussing over normal muscles in a chest with consolidation or pleural effusion.
- **Dullness:** A dull, flat sound is produced on percussion if the underlying lung has massive pleural effusion or mass lesion.
- **Coin test:** In a chest having pneumothorax, a resonant metallic sound is heard with a stethoscope when a coin taps on another coin placed on an interspace.

Auscultation Auscultation of the chest should be performed with the age appropriate stethoscope (one should be familiar with various chest pieces available for different age groups). The diaphragm of the chest piece is used for preferentially hearing high pitched sounds and the bell for low pitched sounds on auscultation. Using an adult stethoscope in a small child may lead to false assessment of adventitious sounds due to poor fit and extraneous sounds.

A pattern should be followed so as not to miss auscultating any part of the lung. It is always preferable to auscultate corresponding areas of the chest on either side in order to compare their symmetry. Remember to auscultate all over, particularly the infraclavicular regions for the upper lobes, the infrascapular regions for lower lobes, and the lower parasternal areas for the right middle or the lingular lobes respectively. To be adequately informative, the auscultatory findings should be recorded in terms of timing (early/late/continuous) and character (fine/coarse) of sounds. Both the breath sounds and adventitious should be noted separately.

Breath Sounds

Vesicular breath sounds These are normal breath sounds heard during respiration in a healthy individual/healthy part of the lung. They are low pitched and longer as well as louder on inspiration. They arise from lobar and segmental airways.

Bronchial breath sounds These are high pitched, louder and may be heard as long in expiratory phase as the inspiratory phase unlike vesicular sounds. They can be heard normally when auscultating directly over trachea, but over rest of the lung field they suggest underlying abnormally like consolidation, cavity and/or collapse.

Bronchophony Transmission of syllables spoken by the child and auscultated on the chest wall as a result of better conductance over a large consolidation. If severe enough, an underlying consolidation may result in transmission of whispered voice, called whispering pectoriloquy.

Adventitious Sounds

Fine crackles Sounds made when previously closed alveoli suddenly reopen during inspiration. Seen with bronchitis, resolving asthma, pneumonia and atelectasis.

Coarse crackles Mainly inspiratory sounds made by movement of fluid in bronchi or bronchioles, typically present in pneumonia.

Wheeze Mostly expiratory continuous musical sounds which are monophonic/polyphonic in character and suggest obstruction to the airflow. They can be biphasic in presence of severe obstruction.

Stridor Monophonic musical sound, high-pitched sound, heard in inspiration.

Pleural rub Patients with pleuritis may have a leathery rubbing sound during inspiration.

Other Signs

Clubbing Clubbing is an important sign in the evaluation of respiratory system and is the result of chronic hypoxia leading to hypertrophy and hypervascularity of distal phalangeal connective tissues. A host of chronic respiratory conditions may lead to clubbing including bronchiectasis, lung abscess, empyema, interstitial lung diseases and pulmonary arteriovenous malformations.

Cyanosis Cyanosis may indicate severe underlying respiratory disorder and is an essential component of respiratory system evaluation. It may not be apparent in the presence of severe anemia. Arterial blood gas analysis may be used to confirm clinically apparent cyanosis.

Pulsus paradoxus This refers to a fluctuation in systolic blood pressure of the child with different phases of respiration, and is measured by finding the difference between systolic blood pressure during inspiration and expiration. It is valuable in evaluation of children with severe asthma.

INVESTIGATION

Imaging

Conventional radiology (X-ray) The knack for reading a chest X-ray is important in developing a clinical acumen as far as respiratory system is concerned. It is the most commonly used investigation for initial evaluation and follow-up of these children. A self-developed and all inclusive systematic approach is required to read a chest X-ray so as to avoid missing out on subtle but important signs. Usually a posteroanterior view and sometimes an anteroposterior or lateral views are ordered. The reader should refer to other detailed texts for X-ray reading skills.

Ultrasonography (USG) Absence of ionizing radiation makes ultrasound an attractive investigative tool for pediatric patients but its current use is limited. The USG image is formed when the sound waves emitted by a transducer are reflected back from the tissues and recorded by another transducer. As air is a poor sound conductor, well-aerated tissue such as lung lacks predictable images on ultrasound. However, non-aerated tissues like pleural fluid, diaphragm and other soft tissues are well examined on USG. Ultrasonography is also useful in evaluation of diaphragmatic lesions, e.g., diaphragmatic hernia. Ultrasound imaging with color flow Doppler is used to diagnose the changes in vascularity of the thoracic and mediastinal lesions.

Chest computed tomography In computed tomography, the image is formed when an anode transmitting X-rays rotates around the body and a battery of detectors record those X-rays. A number of images thus formed are combined to form a cross-sectional image of the patient at that position. CT is most useful to study the anatomy of the upper and lower respiratory tracts as well as lung parenchymal and mediastinal anomalies. A high resolution CT (HRCT) is particularly useful to diagnose diffuse disorders such as interstitial lung disease or bronchiectasis. This, however, has high radiation cost and therefore should be used only where necessary and useful.

Fluoroscopy Fluoroscopy uses the X-rays which upon reflection from a patient are converted into an image by an image intensifier and can be viewed live. It is particularly useful in diagnosing extrinsic tracheal compression by a foreign body or lymph node.

Nuclear medicine or radioisotope studies Nuclear medicine imaging, utilizes the principle that the organ of interest takes up the radiation emitted by a patient when a radiation emitting

substance is administered to him and an image of the organ is formed by a scintillation camera. Positron emission tomography (PET) detects foci of infections and tumors when a radioisotope, fluorodeoxyglucose (FDG), having the same utilization rate as glucose, gets accumulated at these sites.

Magnetic resonance imaging (MRI) MRI is one of the less commonly preferred imaging modality for diagnosis of pulmonary pathologies. Radiofrequency waves reflected from a patient lying in a strong magnetic field are collected and processed to form images using tissues as a contrast.

Angiography and interventional radiology Pulmonary vascular malformations can be diagnosed as well as treated by angiography which uses fluoroscopy. Interventional radiology is used to perform percutaneous drainage of complicated empyema, lung or mediastinal abscesses or percutaneous lung biopsy under fluoroscopic guidance.

Pulmonary Diagnostic Procedures

Thoracentesis This is a diagnostic procedure involving percutaneous insertion of a needle into the pleural space to obtain pleural fluid for cytology and biochemical examination. It may be preceded by a chest X-ray or ultrasound of the chest to visualize the location and volume of collection, particularly if there is a suspicion of very little fluid or a loculated empyema.

Pulmonary function testing Pulmonary function testing helps to differentiate between obstructive or restrictive nature of respiratory disorder and to monitor adequacy of treatment.

Most commonly used method for airway obstruction monitoring is measurement of peak expiratory flow rate (PEFR). The diurnal variation and comparison of child's PEFR with expected PEFR can be used to classify and monitor asthma control at home. The expected PEFR can be deduced from age, sex, height and race specific PEFR standards or by using child's own personal best measured in asymptomatic period. PEFR is reduced and diurnal variation is increased in obstructive lung diseases like asthma. Other spirometry measurements require the child to maximally inhale up to total lung capacity and then exhale as far and as fast as possible. Good spirometry examination requires patient cooperation and it may be difficult to perform in very young children. The forced expiratory volume in 1st sec (FEV₁) is important marker and its decrease correlates with severity of obstructive diseases. The ratio of FEV₁/FVC should be > 90% in normal children. Any reduction in this ratio indicates obstructive lung disease. The average flow rate between 25% and 75% of forced vital capacity is a more reliable indicator of smaller airway obstruction. Restrictive lung disease shows normal FEV₁ with reduced FVC. The diffusing capacity of the lung for carbon monoxide (DLCO) can be used to measure gas diffusability across the alveolar-capillary membrane.

Bronchoscopy Bronchoscopy allows for direct visualization of both upper and lower airways. Bronchoscopy has both diagnostic and therapeutic importance in pulmonary medicine. Diagnostic bronchoscopy allows for collection of specimens by bronchoalveolar lavage, bronchial brushings and tissue biopsies. Indications for diagnostic bronchoscopy include—upper airway obstruction, recurrent pneumonia, persistent pneumonia, foreign body inhalation, hemoptysis, congenital anomalies, and for sample collection in suspected tuberculosis. Hemodynamic instability, bleeding disorders, hypoxemic states, severe obstructive disease, and massive hemoptysis are relative contraindications for bronchoscopy.

The bronchoscope can be flexible or rigid. A rigid bronchoscope is passed through the mouth therefore it yields a better view of the posterior aspect of larynx and trachea, whereas

the flexible bronchoscope gives a better view of the anterior part of the larynx and upper trachea because it is introduced through the nose. Flexible bronchoscopy is especially useful in examination of the lower airways in an intubated patient without the need for extubation and a patient in whom there is an unstable cervical fracture, cervical ankylosis, or mandibular hypoplasia. However, rigid bronchoscope can be more advantageous in certain conditions such as extraction of the foreign body and the evaluation of patients with suspected H-type tracheoesophageal fistula, laryngoesophageal cleft, and bilateral abductor paralysis of the vocal cords.

Sputum Examination

Sputum examination is an important component of pulmonary diagnostics. However, the collection of sputum samples poses difficulties especially in younger children. Sputum induction using nebulization with hypertonic saline can be done if the child is unable to produce sputum. Sputum is then examined microscopically for the presence of neutrophils, eosinophils, macrophages (using Giemsa and Wright stain) and bacteria (using Gram and ZN stain) as well as by microbiologic method (using bacterial and mycobacterial culture methods).

IN A NUTSHELL

1. The approach to a child with a respiratory disorder starts not with auscultation but a detailed history. A thorough examination including inspection, palpation and percussion is an essential component of evaluation, as is general examination and evaluation of upper airway.
2. While examining a child with respiratory disorder stabilization of airway and breathing should be the foremost priority.
3. A familiarity with diagnostic procedures is critical to a complete evaluation of the respiratory system, especially when a thorough history and examination fails to provide all necessary information to arrive at a diagnosis and plan appropriate management.
4. Complex pleural effusions are best evaluated with ultrasonography.

MORE ON THIS TOPIC

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Chapter 39.3

Congenital Malformations of the Upper Respiratory Tract

D Vijayasekaran

Respiratory tract can be broadly considered under two anatomic parts namely the extrathoracic airway and intrathoracic airway. Extrathoracic airway can be considered as upper respiratory tract. It extends from the nose to the mid-trachea (thoracic inlet) which includes nose, nasopharynx, larynx and upper trachea. Obstruction of extrathoracic airway results in inspiratory stridor with prolongation of inspiration. From the management point of view, intrathoracic airway can be divided into intrathoracic-extrapulmonary airway (extends from mid-trachea to the main stem bronchi) and intrathoracic-intrapulmonary airway (extends from secondary bronchi including lung parenchyma). The partial obstruction of intrathoracic airway is characterized by wheeze and prolonged expiration.

DIAGNOSTIC EVALUATION

Congenital malformations of nose, nasopharynx, larynx and upper trachea pose a medical emergency as they invariably compromise the respiratory function. Nasal malformations include arhinia (congenital absence of the nose), nasal hypoplasia, congenital defects of the nasal septum, choanal atresia, and congenital midline nasal masses (dermoids, gliomas and encephaloceles). Laryngopharyngeal malformations include hypoplasia of midface, laryngomalacia, congenital vocal cord paralysis, and laryngocele, etc.

The diagnostic evaluation of a child with suspected congenital malformations of the upper respiratory tract should begin with detailed clinical history including perinatal history. Symptoms that arise immediately after birth or within first few months are invariably due to congenital cause. The clinical features of upper respiratory tract compromise include increased inspiratory effort, stridor, and change in voice. Nasopharyngeal malformations are often associated with dysmorphism. Pharyngeal airway pathology (hypopharyngeal hypotonia) worsens during sleep whereas obstruction of the laryngeal lesions worsens when awake, particularly after exertion.

In addition to thorough clinical history and physical examination, imaging studies, CT scan, laryngoscopy, fiberoptic bronchoscopy and barium swallow play an important role in the diagnosis of congenital malformations of the upper respiratory tract. A three-dimensional image reconstructed from the CT is useful in stenotic lesions. Fiberoptic bronchoscopy is considered as gold standard tool in the diagnosis of anomalies with dynamic movements like laryngomalacia or tracheomalacia. Fiberoptic bronchoscopy under local anesthesia with video monitoring has the ability to directly see upper airway anatomy and function and make an accurate diagnosis and also demonstrate the dynamic movements.

The common upper respiratory tract congenital lesions like choanal atresia, laryngomalacia, vocal cord paralysis, laryngeal web and congenital subglottic stenosis are discussed here.

CHOANAL ATRESIA

Choanal atresia is the most common congenital anomaly of the nose that may be *unilateral* or *bilateral*. Unilateral choanal atresia may be missed for a long time. Newborns are obligate nasal

breathers and nasal obstruction can lead to airway compromise. Baby with a unilateral choanal atresia may cry vigorously and develop respiratory distress particularly after viral infection, because of respiratory compromise. Mouth breathing during cry may relieve the distress and the above cycle may continue. High index of suspicion helps in early diagnosis. Difficulty in passing a catheter through the nostril into the nasopharynx may give a clue to the diagnosis.

Bilateral choanal atresia will be diagnosed early as the baby develops respiratory distress and cyanosis soon after the birth. Typically, such babies have intermittent cyanosis which improves on crying. They may also have pursing of the lips as they work hard to breathe through a closed mouth. In majority of cases (90%) the obstruction in bilateral variety is bony and also associated with anomalies. About 10–20% of patients with choanal atresia have the CHARGE association (coloboma, heart disease, atresia choanae, retarded growth and development or CNS anomalies or both, genital anomalies or hypogonadism or both, and ear anomalies or deafness or both). Mutations in the *CHD7* gene have been linked with CHARGE syndrome.

It can easily be suspected at birth if one notices an inability to pass a nasogastric tube (6 French size for a term neonate) through both sides of the nose. Both fiberoptic rhinoscopy and CT scan help in confirming the diagnosis. Transnasal repair is the treatment of choice in unilateral obstruction. Bilateral atresia may present as life-threatening problems warranting an emergency tracheotomy at times. Mitomycin C has been used to help prevent the development of restenosis.

LARYNGOMALACIA

Laryngomalacia (congenital laryngeal stridor) is the most common congenital laryngeal anomaly, which causes stridor in infants. Immaturity of cartilage results in collapse of supraglottic structures (arytenoids, epiglottis, and aryepiglottic folds) inwards during inspiration and results in low-pitched inspiratory stridor which worsens with agitation, crying and feeding. The noisy breathing in infants with laryngomalacia improves with sleep or prone position.

The symptoms usually become apparent by 2 weeks of age, worsen during first few months and then generally resolve by 12–18 months of age. If stridor presents in the first week of life anomalies other than laryngomalacia should be suspected and investigated for. This is important because these mimickers may need definitive interventions unlike laryngomalacia. The diagnosis is confirmed by outpatient flexible laryngoscopy or bronchoscopy. Epiglottis is omega shaped (**Figs 1A and B**) due to shortened aryepiglottic folds or it may bend over the glottis. Children with mild laryngomalacia (majority) will only have stridor without any other serious symptoms. In severe cases, the entire supraglottic structures may sink into the glottic opening with apparent life-threatening events. Supraglottoplasty is the surgical option for severe laryngomalacia.

Since the noisy breathing can be very loud and alarming, it can make the parents of affected child over anxious requiring repeated reassurance to them, explaining the harmless nature of the problem. Since significant proportion of infants with moderate to severe laryngomalacia are associated with synchronous airway anomalies, it is recommended that complete evaluation of lower airway with bronchoscopy be advised especially when they present with frequent attacks of wheeze and respiratory distress.

CONGENITAL LARYNGEAL WEB

Laryngeal webs are rare congenital anomalies of the larynx. Incomplete recanalization of the laryngotracheal tube during the

third month of gestation leads to different degrees of laryngeal webs. Laryngeal webs are located commonly in the glottic area and are anteriorly placed, leaving a concave posterior glottic opening (**Figs 2A and B**). Laryngeal webs may occur in the posterior interarytenoid, in the subglottic or supraglottic area. The extreme of this situation is complete laryngeal atresia.

Symptoms of laryngeal webs vary from mild dysphonia to significant airway obstruction, depending on the size of the web. Stridor is rare except in patients who have a posterior interarytenoids web. One-third of children with laryngeal webs have associated anomalies of the respiratory tract (commonly subglottic stenosis). When respiratory distress is disproportionate to that caused by the web itself, other anomalies should be suspected.

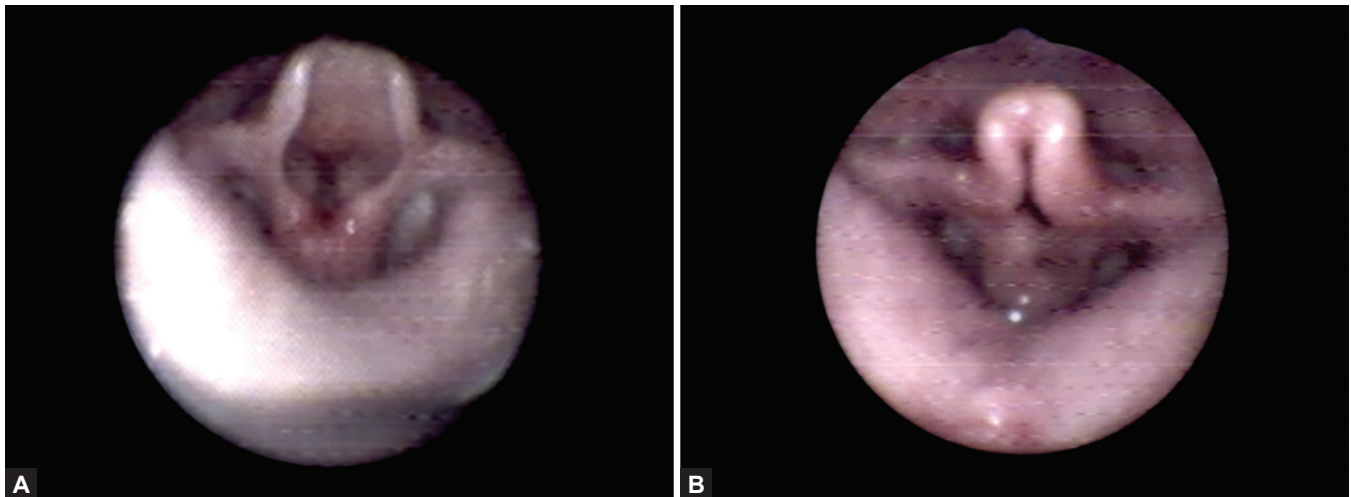
Laryngoscope or fiberoptic bronchoscopy may reveal the presence of a laryngeal web, which may appear as a thin, translucent defect (**Figs 2A and B**) involving the anterior vocal cords which can be released by simple surgery. Laryngeal webs presenting as a thick fibrous structure that extends inferiorly into the subglottic area (associated with subglottic stenosis) are likely to require cartilage augmentation of the cricoid cartilage (laryngotracheal reconstruction).

CONGENITAL VOCAL CORD PARALYSIS

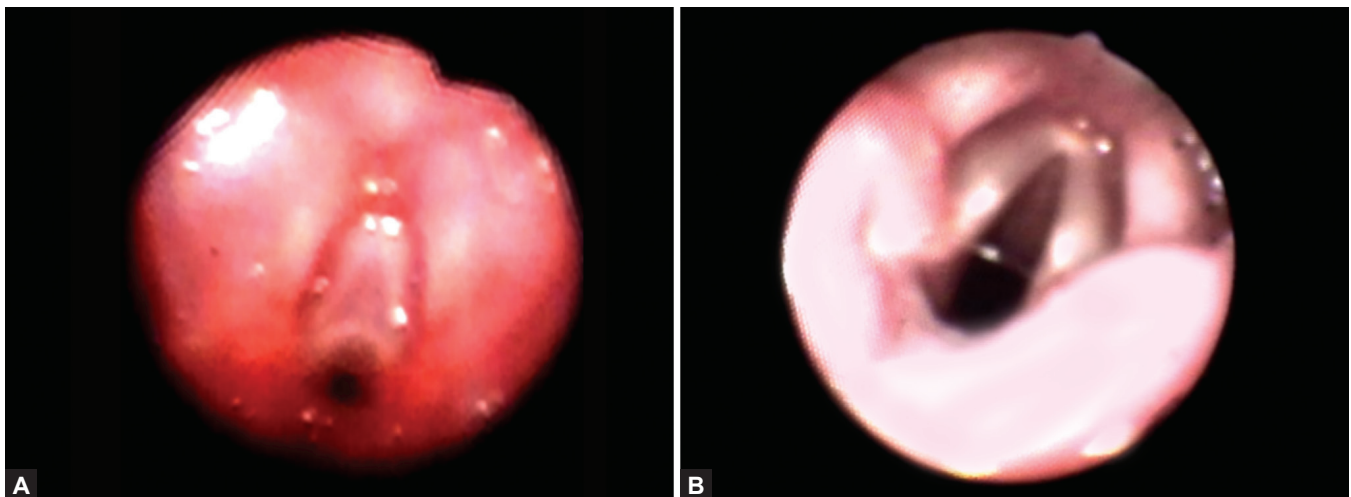
Congenital vocal cord paralysis is one of the laryngeal anomaly, may be bilateral or unilateral. Signs and symptoms of vocal cord paralysis depend on whether the paralysis is unilateral or bilateral.

Congenital bilateral vocal cord paralysis (more common) produces high-pitched inspiratory stridor, and choking with severe respiratory distress. Birth trauma that causes excessive strain to the cervical spine may cause transient bilateral vocal cord paralysis. Bilateral vocal cord paralysis is usually associated with congenital lesions of the central nervous system like hydrocephalus, myelomeningocele, and Arnold-Chiari malformation.

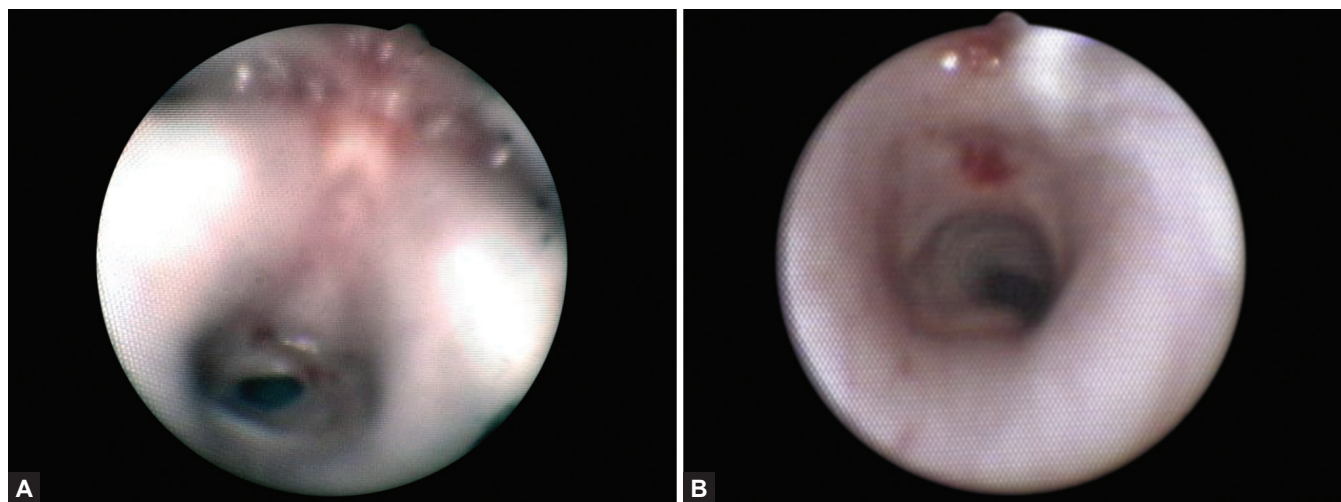
Unilateral vocal cord paralysis may manifest during the first few weeks of life, or it may go unnoticed. Unilateral vocal cord paralysis may occur due to injury of the recurrent laryngeal nerve following surgical management of cardiac anomalies. Unilateral vocal cord paralysis manifests as inspiratory stridor, coughing with frequent aspiration. The diagnosis is made by flexible bronchoscopy or laryngoscopy when the child is awake. Cardiac and neurological evaluation should always be done to rule out the associated congenital anomalies.



Figures 1A and B Bronchoscopic view. (A) Normal larynx; (B) Laryngomalacia



Figures 2A and B Bronchoscopic view. (A) Laryngeal web; (B) Normal vocal cord



Figures 3A and B Bronchoscopic view. (A) Subglottic stenosis; (B) Normal subglottis

Congenital vocal cord paralysis in infants usually resolves spontaneously within 6–12 months. In bilateral vocal cord paralysis, if the obstruction is severe tracheotomy may be indicated.

CONGENITAL SUBGLOTTIC STENOSIS

Congenital subglottic stenosis is the third most common laryngeal anomaly. The subglottis extends from the lower surface of the true vocal cords to the lower surface of the cricoid cartilage. A diameter of (subglottis) 4.0 mm is considered the lower limit of normal in a full term infant and 3.5 mm in a premature infant. Being a fixed obstruction, the stridor produced by congenital subglottic stenosis will be biphasic or primarily inspiratory.

Subglottic stenosis is considered congenital if there is no past history of endotracheal intubation or other forms of laryngeal trauma and approximately 90% of cases manifest in infancy. If the stenosis is severe and congenital, the baby will present with respiratory distress at birth. Viral respiratory tract infections may manifest the congenital subglottic stenosis. One millimeter of edema circumferentially in the subglottis reduces the cross-sectional area by 60%. The edema associated with viral infection is a medical emergency because it may compromise the already narrowed airway. A bronchoscopic view of subglottic stenosis is provided in **Figures 3A and B**.

At times differentiating congenital from acquired subglottic stenosis is difficult if the neonate is subjected for emergency intubation. Majority of subglottic stenosis are acquired and the most common cause is due to endotracheal intubation and the associated inflammatory-type response. The important risk factors are size of the endotracheal tube, the duration of intubation, traumatic intubation, and number of re-intubations.

Since congenital subglottic stenosis is associated with other congenital malformations a thorough search should be done. Cricoid split (anterior laryngotracheal decompression) or laryngotracheal reconstruction with cartilage grafting is usually effective in avoiding tracheostomy. Cricoid split (anterior or multiple cricoid splitting) with cartilage graft interpositioning is usually effective and avoids tracheostomy.

IN A NUTSHELL

1. The important congenital lesions of upper respiratory tract include laryngomalacia, vocal cord paralysis, and laryngeal web subglottic stenosis and choanal atresia.
2. Inspiratory stridor, dysphonia suggests upper respiratory tract pathology.
3. Laryngomalacia is harmless condition presenting with audible stridor in infants.
4. Unilateral choanal atresia may be missed for a long time but the bilateral one presents as a neonatal emergency.
5. Laryngeal web is a rare anomaly with symptoms varies from mild dysphonia to significant airway obstruction.
6. Congenital bilateral vocal cord paralysis is usually associated with congenital lesions of the heart and central nervous system. Subglottic stenosis presents with biphasic stridor.
7. Radiograph of neck, CT scan neck and thorax, fiberoptic endoscopy and barium esophagram are the useful investigations to confirm the diagnosis.

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Chapter 39.4

Epistaxis

Jagdish Chinnappa

Epistaxis (bleeding from the nostril), referred to as *Nasagata Raktapitta* in *Charaka Samhita* and other ancient texts, originates from the Greek *epi* meaning upon and *Stazin* meaning to drip. Most children will experience at least one episode of epistaxis, usually after the age of 2 years. Epistaxis is unusual in children younger than 2 years. Most bleeds are without any obvious etiology (primary) while others are secondary to a systemic disease (e.g., hematological) or a local pathology (e.g., nose picking). Children with recurrent attacks of bleeding need to be diagnosed accurately and managed appropriately. Many children who have recurrent idiopathic epistaxis tend to get better in adolescence.

CLASSIFICATION

Anterior bleeds are easily visible and originate from the Little area. This area is copiously supplied by blood vessels (Kiesselbach plexus) and is one of the most common sites of bleeds. Bleeding can also start from the inferior turbinate.

Posterior bleeds originate from the posterior part of the nose from the distribution of the sphenopalatine artery. This site of bleeding is characteristic of angiofibroma, seen in adolescent boys. The Woodruff plexus located in the posterior part of the inferior meatus and can produce venous bleeding.

Recurrent epistaxis Children with bleeding tendencies or nasal pathology present with recurrent bleeding. Causes of recurrent bleeding are summarized in **Figure 1**.

CLINICAL EVALUATION

Initial Evaluation

Initial assessment should aim to rule out signs of serious disease or hemodynamic alteration. Protecting the airway is vital in posterior nasal bleeds. A careful history and examination is essential to distinguish between a primary and secondary bleed. Concomitant presence of skin and/or retinal bleed should raise the suspicion of a serious underlying disease with hematological abnormality due to defects of bleeding (thrombocytopenia) or coagulation. Epistaxis during febrile illness may be a pointer to dengue, malaria, meningococemia or septicemia. Often, the children may

bring up the swallowed blood in the vomitus and this should be differentiated from other sicker children who may be bleeding from several sites due to a generalized disorder. A careful evaluation of the nose will provide invaluable clues to the etiology.

Nasal Examination

Asymmetry, swelling and discoloration of external nares may suggest a hematoma or ethmoidal disease. The anterior nares (Little area) should be looked for active bleeding and crusting. History of a unilateral discharge with blood stain, masquerading as epistaxis may indicate a nasal foreign body. Rarely a telangiectasia may be seen suggesting a systemic disease. Airflow through the nares should be evaluated by compressing alternate nares. Blockage of the nares may be associated with choanal stenosis, deviated nasal septum, a tumor (angiofibroma) and adenoidal hypertrophy.

Most bleeds are single, unilateral and mild and usually have a benign course. Recurrent mild bleeding from the anterior part of the nose is usually due to excessive drying, trauma from nose picking, and allergic rhinitis. History should be sought about exposure to drugs like aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), warfarin and other anticoagulants; improper use of nasal sprays used for the management of allergic rhinitis; or sniffing of illicit drugs as these can predispose to nasal bleed.

Systemic Evaluation

A general physical examination should evaluate for pallor, telangiectasia, purpura, lymph node enlargement, any other cutaneous, mucous or retinal bleed. Systemic examination should focus on hepatosplenomegaly. Disorders of platelets (deficiency or function defects) and coagulopathy (**Table 1**) can often present as nasal bleed; these should be investigated [e.g., platelet count and peripheral smear, prothrombin time and activated partial thromboplastin time (aPTT)], based on available clues from history and examination.

Epistaxis in infancy is most often due to a secondary cause. Congenital syphilis, diphtheria, trauma to nasal passage by tubes, vigorous aspiration of nasal passages and great vein of Galen malformation are some unique causes in this age group.

INVESTIGATIONS

Investigations are indicated in following situations:

- Episode of severe bleed that alters hemodynamic status and is difficult to control
- Recurrent epistaxis
- Posterior epistaxis

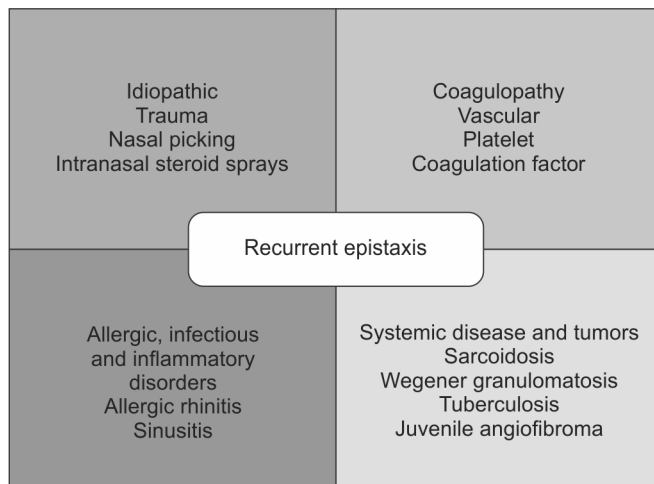


Figure 1 Etiology of recurrent epistaxis

Table 1 Disorders of bleeding and coagulation which may present as epistaxis

Ehler-Danlos syndrome
Hereditary hemorrhagic telangiectasia
Scurvy
von Willebrand disease
Glanzmann thrombasthenia
Bernard-Soulier syndrome
Platelet storage pool diseases
Gray platelet syndrome
Wiskott-Aldrich syndrome
Immune thrombocytopenia
Hemophilia A
Hemophilia B
Factor 5 deficiency
Liver cell failure/renal failure/DIC

- Epistaxis in infants
- Epistaxis part of systemic disease
- Epistaxis that appears for the first time in adolescence.

The most important investigation is visualization of the nasal passages. A flexible rhinoscopy (2.4–3 mm) with adequate suction may reveal the site of bleeding. Sometimes it may be prudent to control the bleeding and do a rhinoscopy in the quiescent stage. Anatomy of the Little area and the Woodruff plexus should be evaluated carefully. In addition, nasal polyp, papillomas, angiofibroma, ulcerated nasal septum as seen in Wegener granulomatosis, and submucosal nodularity seen with sarcoidosis can be identified easily. Radioimaging is valuable in posterior bleeding. It should be done in cases of trauma, suspected neoplasm or if the epistaxis is recurrent and significant.

Coagulation Work-up

Children with recurrent epistaxis without a clear secondary cause should be investigated for a coagulation disorder. Vessel wall anomalies like Ehler-Danlos syndrome, hereditary hemorrhagic telangiectasia and scurvy can be diagnosed clinically. Complete blood count and peripheral smear evaluation will help in the diagnosis of thrombocytopenia and platelet morphology. Platelet function tests should be done when there is a high index of suspicion. Coagulation factor deficiencies are uncommon, when the only manifestation is epistaxis. In select cases, where the bleeding is particularly severe or prolonged, a complete coagulation factor study is indicated. Two of the commonly identified disorders in children with recurrent *idiopathic* epistaxis are von Willebrand disease and hereditary hemorrhagic telangiectasia.

MANAGEMENT

Acute Bleeding

Pressure on the nares in cases of acute bleeding, making the patient bend forward and pinching the nares for about 10 minutes will stop the bleeding in most cases. *Local vasoconstriction* with use of oxymetazoline HCL (0.25, 0.5 or 1%) or phenylephrine drops may help. Excessive use of these should be avoided as it may lead to headaches, dizziness and rarely arrhythmias. Topical anesthesia and nasal packing with or without matrix sealant is useful in most cases with significant bleed, and milder cases not responding to above measures. *Fluid resuscitation* and blood (or its components) replacement may be needed depending upon the severity and cause of bleed. Rarely *endoscopic ligation* of the bleeding artery or *arteriography* with embolization may be needed in extreme cases.

Recurrent Anterior Bleeding

When the patient presents with recurrent epistaxis, identification of the site of bleeding is vital. Simple measures like humidification of the child's bedroom and saline nasal drops 3–4 times a day

will prevent drying and crusting. Application of petrolatum jelly (Vaseline) on the vascular area was advised often but has not been shown to be better than placebo. An antiseptic cream (mupirocin, neomycin) twice a day for 4 weeks will be helpful in many cases. Application should be done with a soft cotton applicator in a gentle manner as rough or forceful application may lead to further bleeding and rarely perforation.

Troublesome recurrent epistaxis may need cauterization of the involved mucosa. An ENT referral may be desirable for thermal or chemical (silver nitrate) cautery. This is an OPD procedure and most children tolerate the procedure well.

Patients with allergic rhinitis on intranasal steroids who develop epistaxis should be asked to discontinue the intranasal steroids till complete cessation of bleeding. They should be instructed on the proper use of the intranasal device.

Recurrent/Severe Posterior Nasal Bleeding

This is a rare situation in children; however an adolescent male with this presentation could have a juvenile angiofibroma. Urgent control of the bleeding by a posterior nasal pack and protection of the airway is vital. An MRI will identify the mass; ENT referral should be done immediately.

IN A NUTSHELL

1. Epistaxis is frequent in children aged 2–14 years.
2. Most cases are benign and local pressure is enough to stop bleeding.
3. Recurrent, severe or posterior bleeding should be investigated.
4. Less severe bleeding disorders like von Willebrand disease and diseases like hereditary hemorrhagic telangiectasia may present as nasal bleed as the predominant symptom.
5. Recurrent, idiopathic anterior bleeding can be managed by local antibiotic creams or cautery.
6. Posterior bleeding in an adolescent male should raise the suspicion of juvenile angiofibroma.

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Chapter 39.5

Allergic Rhinitis

Ankit Parakh, Varinder Singh

Rhinitis is an inflammation of the lining of the nasal cavity. It may affect up to 40% of the general population. The most common form of rhinitis is allergic rhinitis, which is thought to affect up to 10–20% of the population. Recent evidence suggests that the prevalence of the disorder might be increasing. Allergic rhinitis may be associated with major impairments in quality of life, sleep and school performance in children.

Earlier allergic rhinitis was thought to be a disease localized to the nasal cavity. However, current understanding suggests that often the whole airway can get involved in the disease process due to physiological, functional and immunological relationships that exist between the upper and lower respiratory tracts. Allergic rhinitis and asthma appear to represent a *unified airway disease* in many children and this needs to be addressed to ensure optimal and management of rhinitis. Since the accompanying sinus epithelia are also usually involved, the term rhinosinusitis is preferred, but is used in context of more severe disease.

PATHOPHYSIOLOGY

A multitude of inflammatory cells, including mast cells, T-cells, B-cells, macrophages, and eosinophils, infiltrate the nasal mucosa when exposed to an inciting allergen. T helper (Th2) cells release cytokines [interleukin (IL)-3, IL-4, IL-5, and IL-13] which increase the production of immunoglobulin E (IgE) antibody by plasma cells that trigger the release of histamine, leukotrienes and other mediators. These factors lead to dilation of arterioles, heightened vascular permeability, itching, rhinorrhea and contraction of smooth muscle. The early phase of the immune response starts a cytokine cascade resulting in a late phase inflammatory response over the next 4–8 hours, which leads to persistence of symptoms.

CLASSIFICATION

Earlier, allergic rhinitis was classified as seasonal, perennial and occupational based on the exposure of the allergen. The implicated allergens in seasonal allergic rhinitis are a wide variety of outdoor allergens such as pollens or molds while indoor allergens such as house dust mites, molds, insects (cockroaches) and animal danders are implicated in perennial allergic rhinitis. However, in certain areas an individual may be allergic to a variety of outdoor pollens and molds and thus may lack seasonality—mimicking perennial allergic rhinitis. On the other hand symptoms of perennial allergy may be present intermittently such as many patients allergic to house dust mites suffer from mild intermittent allergic rhinitis (IAR). Some patients might have baseline symptoms with perennial allergic rhinitis and also experience seasonal superadded exacerbations when exposed to pollens or molds. Given this variety of responses, this classification has been found to be unrealistic.

Allergic Rhinitis and its Impact on Asthma (ARIA) group proposed a new classification (**Table 1**) for allergic rhinitis. It is now reclassified as IAR and persistent allergic rhinitis (PER) and the severity of the disease is classified as mild or moderate/severe. The terms “IAR” and “PER” are not synonymous with *seasonal* and *perennial* as they do not represent the same stratum of the disease.

Table 1 Classification of allergic rhinitis according to ARIA

Intermittent	Symptoms are present < 4 days a week or for < 4 consecutive weeks
Persistent	Symptoms are present > 4 days a week and for > 4 consecutive weeks
Mild	<i>None of the following items are present:</i> Sleep disturbance Impairment of daily activities, leisure and/or sport Impairment of school or work Symptoms present but not troublesome
Moderate to severe	<i>One or more of the following items are present:</i> Sleep disturbance Impairment of daily activities, leisure and/or sport Impairment of school or work Troublesome symptoms

Abbreviation: ARIA, Allergic Rhinitis and its Impact on Asthma.

CLINICAL FEATURES

The symptom complex of allergic rhinitis includes: nasal congestion, nasal itch, rhinorrhea and sneezing. The duration and frequency of symptoms including the effect on the quality of life requires evaluation to classify the severity of rhinitis. Associated ocular symptoms like conjunctival erythema, watering and itching of the eyes suggest an associated allergic conjunctivitis. Symptoms suggestive of associated bronchial asthma like chronic cough, wheezing, breathlessness, etc., should also be elicited. History of persistent mouth breathing, snoring and damp voice would point toward an adenoid enlargement. Hearing should also be evaluated for associated serous otitis media. Personal history of past or ongoing atopic dermatitis should also be evaluated. Family history of any atopic disorder should be elicited. Symptoms of comorbidities as sinusitis, conjunctivitis, asthma should also be asked for. A detailed evaluation of the patient environment is recommended (home, school) to determine potential triggers of the child's rhinitis. The commonly offending allergens include pollens, animal fur and tobacco smoke, mosquito coils and house dust mites.

Physical examination should particularly identify evidence for possible mouth breathing, transverse nasal creases secondary to regular rubbing of the nose, frequent throat clearing suggesting a postnasal drip, and allergic shiners (discoloration and swelling under the eyes). Nasal examination should focus on turbinate hypertrophy, pale mucosa, deviated nasal septum and any polyps. Ears should also be evaluated although usually they are normal. Some children can have a serous otitis media associated with adenoid enlargement, which requires assessment of the tympanic membrane for eustachian tube dysfunction. Sinuses should be palpated for tenderness for sinusitis. Posterior oropharynx should be evaluated for any postnasal drip and tonsillar enlargement. Detailed chest examination for wheezing and skin for atopic disease should also be done in all cases.

DIFFERENTIAL DIAGNOSIS

The important causes of childhood rhinitis can be classified as allergic, nonallergic and infective. Conditions that mimic allergic rhinitis, such as nasal foreign bodies, partial choanal atresia, cerebrospinal fluid (CSF) rhinorrhea, primary ciliary dyskinesia and laryngopharyngeal reflux, should be carefully looked for. Some children suspected to have mimickers of allergic rhinitis might need further investigations including a sweat test, immunological work-up, CT of paranasal sinuses, and nasal endoscopy. Adenoid

hypertrophy and deviated nasal septum are conditions which can coexist with allergic rhinitis.

TREATMENT OF RHINITIS

The goals of treatment in children with allergic rhinitis as in any chronic disease are to achieve good symptom control with least adverse effects secondary to drugs. The cornerstones of therapy to achieve these goals include allergen avoidance measures, intranasal corticosteroids, oral antihistamines, leukotriene receptor antagonists, and immunotherapy. Since many children with allergic rhinitis would have associated asthma, a *unified airway disease* evaluation and treatment of asthma is important.

Allergen Avoidance

Allergen avoidance measures can significantly improve symptoms. Parents and children should be counseled regarding these. The importance of the avoidance of common household allergens like house dust mites, molds, pets, pollens and tobacco smoke should be advised. A combination of these measures lead to optimal results. The patients allergic to house dust mites are often advised to use allergen-impermeable bedding covers but recent studies and meta-analysis have not shown this to be useful. Bed and linen should be washed in hot water and blankets should be kept in sunlight weekly. Exposure to outdoor allergens (pollen and molds) can be decreased by minimizing opening of windows, using an air conditioning, and reducing the time spent outdoors. Removal of the offending pet would be required in children who are allergic to animal fur. Many patients would experience good symptomatic relief with allergen avoidance alone, although some children continue to have persistent symptoms despite avoidance of allergen and trigger. Even in these children allergen avoidance would reduce the drugs required to achieve good control.

Oral H₁ Antihistamines

First-generation antihistamines (chlorpheniramine, diphenhydramine) have sedative properties and can reduce work performance. Oral second-generation antihistamines (detailed in **Table 2**) are better tolerated with fexofenadine having the least sedating potential. These drugs also do not cause significant QT prolongation and have no major drug interactions.

Antihistaminics have found to be more effective than placebo and can reduce the total nasal symptom scores by 7 (5–9)%. Antihistaminics are more effective on neurally-mediated symptoms like itch, sneeze and rhinorrhea with only a modest effect on nasal blockage. Regular therapy with second generation antihistaminics is more effective than *as-needed* use in children with persistent symptoms.

Nasal H₁ Antihistamines

The therapeutic effects of intranasal antihistaminics (azelastine, olopatadine) are superior to oral antihistamines for control of nasal symptoms but being topical they do not improve symptoms at other sites (conjunctivitis, postnasal drip, urticaria). The onset of action is quick (within 15 min) and hence these are useful for acute symptomatic relief. The major drawbacks are the local irritation and the taste disturbance with azelastine. Antihistaminics are the therapy of choice for mild to moderate intermittent and mild PER. They can also be used as add on therapy to intranasal corticosteroids (INCS) for children with

moderate to severe persistent rhinitis which is uncontrolled on INCS alone.

Intranasal Corticosteroids

Intranasal corticosteroids are the most effective available therapy for allergic rhinitis and are shown to be superior to antihistamines in meta-analysis. They suppress inflammation in the inflammatory cascade at multiple points. As compared with placebo, the reduction in the symptom score with INCS is 17% more. INCS are the therapy of choice for (1) moderate to severe PER, (2) in all children presenting with rhinitis associated with nasal polyps, and (3) for those who have inadequate response to oral/intranasal antihistamines alone. Adverse effects are less common (seen in < 10% cases) and include nasal irritation, sore throat and nasal bleeding. Reduction in the local adverse effects can be achieved by the correct use of the intranasal spray. Hypothalamic-pituitary-adrenal (HPA) axis suppression can occur when concomitant inhaled steroids are also used in high doses along with INCS. Fluticasone furoate and mometasone are approved above the age of 2 years, fluticasone propionate above the age of 4 years, and budesonide/ciclesonide above the age of 6 years. Budesonide is now not preferred as its high bioavailability can lead to more systemic side effects. Otherwise all INCS have comparable efficacy at equipotent doses.

Oral Corticosteroids

Oral steroids are rarely required for the treatment of children with allergic rhinitis, except in cases of severe disease for short-term rescue medication. A short course of oral steroids at a dose of 0.5 mg/kg can be used for 5–7 days in combination with INCS.

Leukotriene Receptor Antagonists

Leukotriene receptor antagonists (LTRA) are less effective than INCS and reduce symptoms scores by 5% less than placebo. The response appears to be variable in children. They appear to have a role in children with asthma associated with rhinitis.

The combination of H₁ antihistaminics and LTRA does not show added benefit to either drug when used alone and hence is not recommended. The combination is also less effective than INCS alone.

Other Drugs

Topical anticholinergics like ipratropium bromide are useful for symptomatic relief for rhinorrhea, but do not have effect on any other symptom. They can be used as an add-on therapy to INCS. The drawback is that it requires thrice daily administration. Intranasal decongestants like xylometazoline increase nasal vasoconstriction and are useful for brief use (typically for < 10 days). Prolonged use of decongestants might lead to rhinitis medicamentosa and hence should be avoided. Oral decongestants like pseudoephedrine are less effective in reducing nasal obstruction but have a longer duration of action.

Allergen Immunotherapy

Immunotherapy has been recommended in children with allergic rhinitis (1) where allergen avoidance is difficult, and (2) who have failed to respond to antihistaminics and INCS. The risk to benefit ratio should be considered in the individual case. The quality of allergen used is extremely important and only standardized extracts should be used. Sublingual immunotherapy (SLIT) is an alternative to subcutaneous immunotherapy and might be beneficial in children. It is performed at few centers in India.

Table 2 Overview of pharmacologic treatment options for allergic rhinitis

Drug	Formulations	Recommended dose	Common adverse effects
Intranasal steroids			
Fluticasone propionate	50 µg	< 12 years: 1 spray in each nostril BD; > 12 years: 2 sprays in each nostril BD	Irritation, epistaxis, HPA suppression in high doses. Usually occurs if receiving inhaled steroids at high doses for associated bronchial asthma
Mometasone	50 µg	< 12 years: 1 spray in each nostril BD; > 12 years: 2 sprays in each nostril BD	
Budesonide	32 µg	< 12 years: 1 spray in each nostril BD; >12 years: 2 sprays in each nostril BD	
Ciclesonide	50 µg	< 12 years: 1 spray in each nostril OD; > 12 years: 2 sprays in each nostril OD	
Fluticasone furoate	27.5 µg	< 12 years: 1 spray in each nostril OD; >12 years: 2 sprays in each nostril OD	
Second generation oral antihistaminics			
Cetirizine	Tablet 10, 20 mg; Syrup 5 mg/5 mL	6 months–2 years: 2.5 mg OD; 2–6 years: 5 mg OD; > 6 years: 10 mg OD	Sedation with some salts is the only adverse effect. Can be reduced with bed time dosing. Headache, GI symptoms, dry mouth can also occur
Levocetirizine	Tablet 5, 10 mg, Syrup 2.5 mg/5 mL	6 months–2 years: 2.5 mg OD; 2–6 years: 2.5 mg OD; > 6 years: 5 mg OD	
Fexofenadine	Tablet 120, 180 mg, Syrup	6 months–2 years: 15 mg BD; 2–11 years: 30 mg BD; > 11 years: 60 mg BD	
Loratadine	Tablet 5 mg	2–6 years: 5 mg OD; > 6 years: 10 mg OD	
Olopatadine	Tablet 5 mg	6 months–2 years: 2.5 mg OD; 2–6 years: 2.5 mg OD; > 6 years: 5 mg OD	
Intranasal antihistaminics			
Azelastine	140 µg	< 12 years: 1 spray in each nostril OD; > 12 years: 2 sprays in each nostril OD Available also as a combination with fluticasone propionate and furoate	Irritation, bitter after taste
Leukotriene receptor antagonists			
Montelukast	4 mg, 5 mg, 10 mg	6 months–4 years: 4 mg; 4–14 years: 5 mg; 14 years: 10 mg	Rarely headache, abdominal pain, dyspepsia, fatigue, dizziness, elevated liver enzymes

Abbreviations: HPA, hypothalamic-pituitary-axis; GI, gastrointestinal.

IN A NUTSHELL

1. Allergic rhinitis is a common chronic disorder in children that can significantly impact quality of life but is under diagnosed.
2. The diagnosis is usually made with a thorough history and examination with investigations required in rare cases of mimickers.
3. The concept of unified airway disease should be remembered and coexisting asthma and sinusitis should be evaluated.
4. The therapies available for the management of allergic rhinitis are effective, and safe and well-tolerated.
5. The main stay of therapy remains as second-generation oral antihistamines and intranasal corticosteroids. Sublingual or subcutaneous immunotherapy might be required in select cases.

MORE ON THIS TOPIC

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Chapter 39.6

Otitis Media

Jagdish Chinnappa

Otitis media is an inflammation of the middle ear cleft, in an otherwise sterile environment, from invasion by either a viral or bacterial pathogen. This is followed by production of an exudative fluid which accumulates in the middle ear cleft, and distends the sensitive tympanic membrane producing the clinical symptoms and signs. The severity and rapidity of progress of the inflammation depends on the virulence of the organism and the inflammatory response. Acute otitis media (AOM) can be classified into *Severe* and *Nonsevere* based on symptoms and signs secondary to this response.

TYPES OF OTITIS MEDIA

Most children are able to effectively clear the inflammation over time, with or without antibiotic treatment but the course can be variable. Some children can run an extremely stormy course, with extension of the infection beyond the middle ear [*Complicated (AOM)*]. There could be extensions into the inner ear, external ear [*Acute suppurative otitis media (ASOM)*] surrounding tissue (mastoiditis) or even intracranial (cerebral abscess, etc.). A few children may continue to retain fluid in the middle ear cleft for prolonged periods of time [*Otitis media with effusion (OME)*]. OME needs to be recognized and followed up as it can lead to hearing aberrations and resultant speech abnormalities in small children.

A very small percentage of children tend to form biofilms in the middle ear cleft. These children may present with intermittent episodes of otitis media with asymptomatic intervals. Children with craniofacial anomalies, defects in immune function, adverse environmental conditions and eustachian tube dysfunction can have repeated episodes.

Chronic suppurative otitis media (CSOM) is a syndrome where there is a perforation of the tympanic membrane and persistent or recurrent purulent drainage from the middle ear. It is a distinct entity with a microbial and management perspective that is very different from AOM.

Table 1 describes the complete clinical spectrum of otitis media. The goals of management should be prevention of complications and hearing loss. This can be achieved by accurate diagnosis, with judicious use of antibiotics (restricting use to only select patients to prevent antibiotic resistance).

EPIDEMIOLOGY

Annually, more than 700 million cases of AOM occur worldwide with half of them occurring in under-fives. The global burden of

illness from CSOM involves 300 million individuals with draining ears with 20% in under-five children. More than half of children with CSOM suffer from significant hearing impairment. India, with 7.8% prevalence of CSOM, ranks second only to Tanzania. Prevalence of acute and chronic otitis media in general population of India ranges from 1% to 1.7% and 1.6% to 4.6%, respectively. Prevalence is much higher in rural areas. In some areas, every third child in a rural population has a discharging ear.

Otitis media is most often seen in young children between the ages of 6 and 18 months. Neonates and infants may have a spectrum of disease ranging from septicemia to asymptomatic middle ear effusion. The disease is seen less commonly and with reduced severity in preschool and school going children. It occurs infrequently in children older than 7 years and is rare in adolescents.

ETIOLOGY

Acute otitis media is often triggered by a viral upper respiratory infection with a background of pathogenic bacteria colonizing the upper respiratory tract. Upper airway colonization with pathogenic pneumococci is known to occur as early as 2 months of age in our country. The viruses most often implicated are the respiratory syncytial virus, rhinovirus, coronavirus, influenza and parainfluenza viruses, and adenovirus. BOCA and Metapneumoviruses are less often involved. Severe virus infections like measles can also predispose to AOM.

Bacteriology of AOM and OME is similar; the most common organisms being *Streptococcus pneumoniae* (40%) followed by *Haemophilus influenzae* (25–30%), *Moraxella catarrhalis* (10–15%) and *Streptococcus pyogenes*. In about 50% cases of OME with effusion, bacteria can be cultured from middle ear fluid. *Chlamydia trachomatis* is incriminated in infants below 6 months of age. Serotypes of *S. pneumoniae* producing otitis media vary region wise. Serotypes 19A, 3, 19F, 6b and 14 are implicated globally.

Nontypeable *H. influenzae* (NTHI) frequently colonizes the nasopharynx in young children. It causes a less severe disease than pneumococcus and is often associated with the conjunctivitis otitis media syndrome. NTHI is implicated in otitis media in all age groups, including adolescents. Many strains of NTHI produce β -lactamase. *Moraxella catarrhalis* is a frequent colonizer of the nasopharynx and produces a milder disease and is a significant pathogen in children with recurrent otitis media. Group A and B streptococci, *S. aureus*, *S. epidermidis* and gram-negative bacteria like *Proteus* and *Pseudomonas* may occasionally cause AOM. *Chlamydia* and *Mycoplasma* may occasionally produce AOM as a part of generalized respiratory infection. Both tuberculosis and nontuberculosis mycobacteria can also produce chronic middle ear disease with frequent involvement of the mastoids.

Otitis media with effusion was considered to be immunological and parainfectious in nature. However, recent studies have

Table 1 The spectrum of otitis media

Condition	Definition
Acute otitis media (AOM)	Acute onset of signs and symptoms of middle ear inflammation and presence of fluid in the middle ear
Resistant otitis media	Inadequate response of the AOM to the initial antibiotic after 72 hours of appropriate treatment
Relapse of AOM	Reappearance of signs and symptoms after initial response during therapy or within 4 days of stopping therapy, indicates that the infection has not been eradicated
Recurrence of AOM	Reappearance of signs and symptoms 5–14 days after therapy ends
Recurrent otitis media	Three or more episodes in a 6-month period or four or more episodes in a year
Otitis media with effusion (OME)	Presence of fluid in the middle ear cleft without signs of inflammation following an episode of AOM. Persistent OME indicates presence of this fluid beyond 12 weeks
Chronic suppurative otitis media (CSOM)	Chronic discharge from the ear following an episode of AOM; Minimum duration 2 weeks; acceptable 6–12 weeks despite medical management

reported microbial pathogen isolation in about half the cases. Various organisms like *S. epidermidis*, *S. aureus*, *Moraxella*, *Streptococcus* sp., NTHI, and *S. pneumoniae* have been isolated. The significance of this isolation is unclear.

Data from many studies from India implicate external ear pathogens like *Pseudomonas aeruginosa*, *S. aureus* and anaerobes in CSOM.

Recurrent otitis media is associated with colonization with NTHI more frequently than controls. Formation of biofilms, presence of intracellular organisms and polymicrobial milieu are some of the other features of middle ear pathology in recurrent otitis media.

PATHOGENESIS

The pathogenesis of OM is a complex interplay of anatomical, functional, immunologic, environmental, microbial and genetic factors (**Fig. 1**). The key event is invasion of the middle ear cleft by microorganisms present in the nasopharynx or rarely through a perforated tympanic membrane. The eustachian tube connects the middle ear to the nasopharynx. It (1) equilibrates pressure between the middle ear and the atmospheric pressure, (2) prevents aspiration of nasopharyngeal contents into the middle ear, and (3) facilitates clearance of fluid from the middle ear. Eustachian tube dysfunction plays an important role in pathogenesis of OM. The eustachian tube is shorter and more horizontal in children making it more vulnerable to aspiration.

Anatomical factors predisposing to otitis media include craniofacial anomalies like Pierre Robin sequence, Down syndrome, Turner and other syndromes. Cleft palate, submucous clefts and bifid uvulas may also predispose to otitis media through alteration of eustachian tube function.

Immune mechanisms play a very important role in initiating, resolving and perpetuating inflammation in the middle ear. Allergic rhinosinusitis is an important predisposing factor for OM. The mechanisms are complex and include inflammation of the respiratory mucosa of the eustachian tube, increased secretions in the nasopharynx facilitating aspiration and circulating inflammatory mediators altering the mucosal dynamics of the eustachian tube. Immune deficiencies impair the clearance of microbes in the middle ear fluid leading to persistence or recurrence of the disease. Mucociliary clearance may be affected

in children with ciliary dyskinesia and cystic fibrosis making them more prone for OM. Bottle feeding, pacifier use and exposure to smoke are high-risk factors for susceptibility to OM. Attendance to day-care centers, exposure to passive smoking, and overcrowding are the other high-risk factors.

CLINICAL FEATURES

Acute Otitis Media

Acute otitis media usually follows an attack of common cold. Symptoms are nonspecific in young children. Irritability, poor feeding, nausea, vomiting, diarrhea, disturbances in sleep are common presenting symptoms. Fever is usually moderate but may not be always there. Ear pain in older children and tugging or repeated painful gestures involving the ear may be seen. Ear pain alone is insufficient to diagnose AOM as it may occur in many other conditions like inflammation in the external ear or referred pain from the dental or pharyngeal structures. Discharge from the ears occurs when there is an acute perforation of the tympanic membrane. Purulent conjunctivitis may be seen in conjunction with otalgia in AOM caused by NTHI organisms.

Symptoms in complicated AOM spread of infection within the ear can produce symptoms of instability and clumsiness, facial asymmetry, swelling in the postauricular space and ringing sound in the ear. Intracranial spread produces symptoms characteristic of the site involved.

Examination may reveal the temperature to be as high as 40°C (104°F). Otoscopy demonstrates congested, i.e., red and bulging tympanic membrane. Most children with AOM are irritable and resist evaluation. Administering an oral analgesic (Paracetamol) prior to evaluation could help. In older children, the opportunity to play with a toy otoscope and doll may reduce apprehension. The child may also present with a discharging ear. Evaluation of craniofacial structures should be done prior to eardrum evaluation. ENT examination should include looking for evidence of allergic disease, obstruction, deviation and polyps in the nose, evaluation of the throat to look for tonsillar and adenoidal hypertrophy, submucous clefts and bifid uvulas. A postnasal drip and discharge may be evident.

Otoscopy

Otoscopy is the most important component of evaluation of OM. There are three main components of doing otoscopy in clinical practice, namely (1) proper visualization and performing a pneumatic otoscopy, (2) interpreting the findings, and (3) recording and following up. For proper visualization it is important to have a good otoscope with pneumatic facility (**Figs 2A to C**), a cooperative patient and knowledge about the anatomy and pathology of the ear drum. Many otoscopes are available with varying light sources, magnification and pneumatic capability.

A systematic examination of the ear drum include position of the drum, its color, opacity and mobility (**Fig. 3**). Evaluation of the tympanic membrane in a crying child may show increased vascularity especially around the handle of malleus. This is not a sign of acute otitis media. A combination of intense erythema, bulging and limited mobility is the hallmark of acute otitis media. In addition to this, it may not be easy to identify the landmarks of the normal drum, a feature called opacification of the drum. Perforation is a late event in an acute otitis media. Hearing loss is usually not complained of by the very young and may not even be noted by the parents.

Otitis Media with Effusion

Most children are asymptomatic but the occasional patient with bilateral disease may have hearing loss, behavioral problems like hyperactivity or speech abnormalities. Rarely tinnitus and

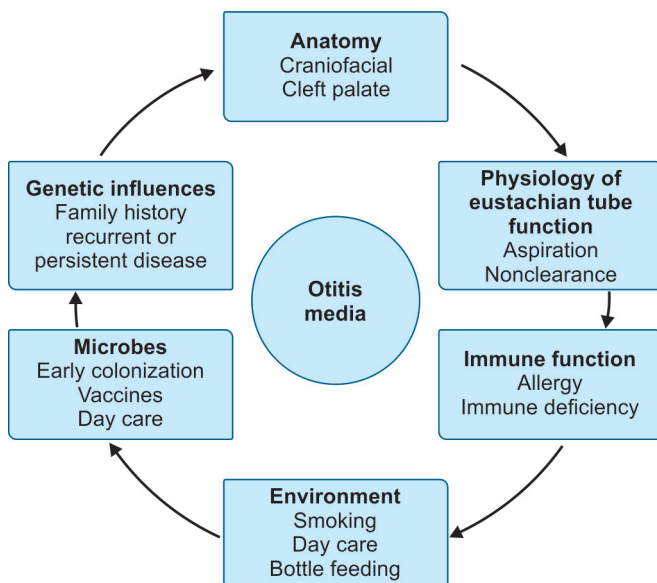


Figure 1 Key issues in pathogenesis of otitis media



Figures 2A to C (A) Otoscope with pneumatic facility; (B) Macro view otoscope; (C) Ear speculum of various sizes and rubber adaptors to facilitate tight seal

vertigo may be the manifestations. Pneumatic otoscopy findings include a full or retracted drum (depending on the type of fluid and chronicity), limited mobility and opacity. Redness and signs of inflammation are not seen.

Chronic Suppurative Otitis Media

There may be discharge, deafness, bleeding, tinnitus, vertigo, and pain. Discharge and deafness are the most common of these, which at times persist for a very long time, even for years. The external ear may have purulent foul smelling discharge. The drum may be opacified, retracted and may reveal a central perforation in pars tensa of the tympanic membrane (*safe type of CSOM*) or a defect in pars flaccida often associated with cholesteatoma (*unsafe type of CSOM*).

COMPLICATIONS

- **Hearing loss:** Most important sequel of otitis media is hearing loss, which usually is of conductive type (because of fluid in the middle ear), but at times can also be of sensorineural type. The initial months of life are important in language acquisition and a child by four years of age produces all the basic syntactic structures that he will ever use. Since so much progress in language acquisition is made during infancy, any problem in receiving or interpreting sound signals will have a significant effect on development of speech and language.
- **Intratemporal complications** include acute and chronic perforation of tympanic membrane, cholesteatoma, mastoiditis, petrositis, labyrinthitis, and facial paralysis.
- **Intracranial extension:** Untreated otitis media, whether acute or chronic, may lead to life-threatening intracranial complications. These include brain abscess, meningitis, extradural abscess, lateral sinus thrombosis, subdural empyema or otitic hydrocephalus.

INVESTIGATIONS

The diagnosis of OM is clinical and most cases do not need any investigations. Severe, complicated, recurrent, persistent or

relapsing cases may need to be evaluated. Careful history and a detailed clinical evaluation will point toward the pattern of investigations needed. Anatomical evaluation of the craniofacies and adenoidal hypertrophy by imaging may be needed in select cases. Nasopharyngoscopy and endoscopy of the eustachian tube may be needed in complex situations. Immune function evaluation may be needed in those with severe nonresponsive disease or with other pointers to immune dysfunction. Functional impairments may have to be evaluated by tympanometry, reflectometry and age appropriate audiometry. These are particularly of value in persistent OME. Tympanometry is an important investigation in OME; persistent OME and recurrent OME.

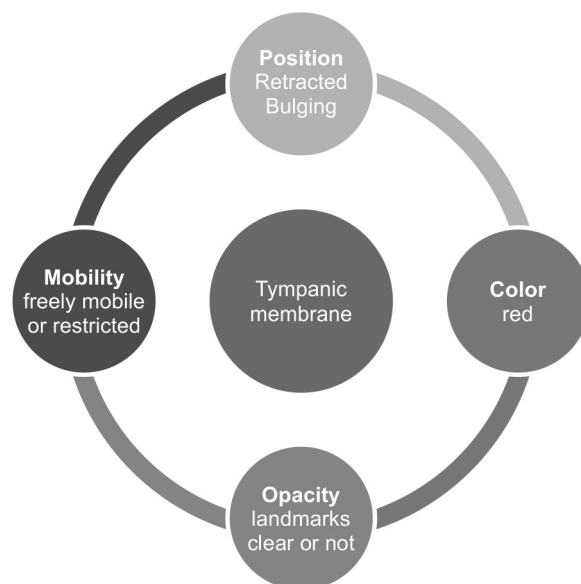


Figure 3 Examination of tympanic membrane

MANAGEMENT

Acute Otitis Media

All children with AOM should be given adequate analgesia and antipyretics. Oral paracetamol and occasionally nonsteroidal anti-inflammatory drugs (NSAIDs) are the agents of choice. Topical anesthetic agents in ear drops may offer temporary relief. Antibiotic ear drops should not be used. Locally active nasal decongestants may be used for short periods.

Antibiotics

There has been considerable revision in the guidelines for antibiotic administration in AOM. The main issues have been the judicious use of antibiotics since many older children with mild or unilateral disease tend to resolve spontaneously. In clinical settings we need to decide on the following parameters:

- Which group of children should be started on antibiotics at diagnosis? Which group of children can be managed by watchful waiting without antibiotics and can be started on antibiotics if the condition worsens?
- Which is the antibiotic of choice?
- For how long should the antibiotic be given?
- How should we manage refractory and relapsing cases?

It may be useful to consider presence of risk factors in the decision making for antibiotic usage (**Figs 4A and B**). Where the decision has been to withhold antibiotics, the parents must be counseled and asked to return for follow-up. Up to one-third of patients may need starting an antibiotic on follow-up at 72 hours.

Choice of Initial Antibiotic

The initial antibiotic of choice should be oral amoxicillin in a dose of 40–50 mg/kg/day in 2–3 divided doses. In areas where pneumococcal resistance to beta lactam is increasing (currently not the situation in India) the dose could be started at 90 mg/kg/day in 2–3 divided doses. Co-amoxycylav (45 mg of amoxicillin/kg/day in 2 divided doses) should be the initial antibiotic of choice in severe disease; or nonresolution of symptoms after 48–72 hours of starting amoxicillin. It is also the initial antibiotic of choice in conjunctivitis otitis syndrome caused by NTHI, or in children with relapse or recurrence of OM after treatment with amoxicillin in the previous 30 days. First and second generation cephalosporins may also be used but are not as cost-effective as the above. Cefixime has

not been shown to clear pneumococcal infections effectively and is not a drug of choice in most situations. Parenteral ceftriaxone (50 mg/kg) in a single dose may be given initially in children who have intractable vomiting and severe toxicity. In children with penicillin allergy type 1 macrolides (clarithromycin or azithromycin) or clindamycin (not active against NTHI) may be used. In penicillin allergy type 2, cefdinir, cefpodoxime and cefuroxime can be used. Commonly used drugs for AOM in children are summarized in **Table 2**.

Antibiotics in Nonresponsive or Relapsing Cases

In children who do not respond to initial antibiotic choice or who relapse soon after stopping, a careful consideration to the causes of nonresponse should be given. Compliance with instructions is a frequent problem. Prolonged exposure to precipitating factors may be another issue. After due consideration of these issues an alternative antibiotic course could be given. Usually the choice of a third generation oral cephalosporin like cefpodoxime or cefdinir is acceptable. A combination of clindamycin (covers pneumococci effectively) with cefixime (covers NTHI) could also be tried. If there is still no response then parenteral ceftriaxone (50 mg/kg/day) for 3 days may be administered.

Other Considerations

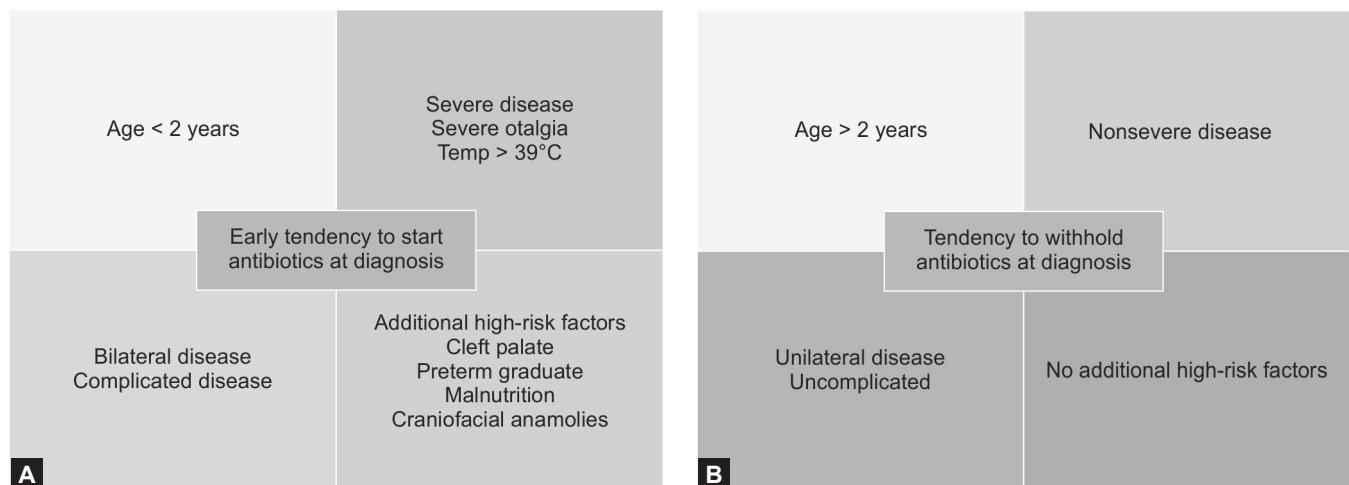
In instances where there is a highly toxic child in severe pain and a red bulging drum, an ENT referral for Myringotomy may be necessary. In children who have frequently relapsing disease, consideration for adenoidectomy and grommet insertion is in order.

Duration of Antibiotics

In children less than 2 years the duration of treatment should be 10 days. In older children between 2 years and 5 years, 7 days of antibiotic usage should be adequate. Above the age of 5 years AOM is uncommon and 5 days of antibiotic should be sufficient.

Management of Persistent OME

Otitis media with effusion is a common sequel of AOM. Most cases resolve spontaneously and need only a careful follow-up. A small percent of children have bilateral fluid collection that persists beyond 12–16 weeks. Some children have intermittent fever, and occasional otalgia. These children may be given a



Figures 4A and B Decision to (A) start antibiotics; or (B) withhold antibiotics in acute otitis media depends on several factors

Table 2 Drugs used for treating otitis media in children

Drug	Dosage Per day	Number of doses	Duration of treatment in < 2 years age	Comments
Amoxicillin	40–90 mg/kg	2–3	10 days	Drug of initial choice
Co-amoxiclav	40–90 mg/kg	2	10	Severe disease, Relapse, Conjunctivitis
Cefaclor	40 mg/kg	3	10	Alternative to amoxicillin
Cefdinir	14 mg/kg	1–2	5/10	Alternative to amoxicillin
Cefpodoxime	10 mg/kg	2	5	Resistant or relapse
Cefuroxime	30 mg/kg	2	10	Resistant or relapse
Azithromycin	10 mg/kg	1	3	Penicillin allergy
Clarithromycin	15 mg/kg	2	10	<i>Mycoplasma</i> or <i>Chlamydia</i> infection
Co-trimoxazole	8 mg/kg of trimethoprim	2	10	High incidence of <i>Pneumococcus</i> resistance
Clindamycin	30–40 mg/kg	3	7–10 days	Useful against resistant <i>Pneumococcus</i>
Ceftriaxone	50 mg/kg	1	3 days resistant or refractory	Parenteral
Levofloxacin	10–20 mg/kg	1–2	5–7	Reserve for drug resistant cases

course of coamoxyclov for 10 days. If hearing loss is significant in these children, there may be a role for myringotomy with grommet insertion. Other forms of medical treatment like antibiotics, decongestants (oral or nasal), steroids (intranasal, oral), and leukotriene antagonists have not been shown to be effective. Careful attention to environmental triggers and optimal management of allergic rhinitis will help a small percentage of children.

Management of CSOM

Chronic suppurative otitis media presents as a chronically discharging ear with hearing loss. Mild cases can be treated with topical quinolone drops and aural toilet. Treatment can be continued till the ear is dry. Closure of perforation by myringoplasty can be considered once the ear is dry. Myringoplasty is usually not undertaken before the age of 10 years due to a high incidence of re-infection and re-perforation in younger children. The only treatment for an unsafe type of CSOM is surgical in the form of mastoid exploration (mastoidectomy).

OUTCOME AND PROGNOSIS

Most children with AOM resolve spontaneously or with appropriate antibiotic treatment. A small percentage may have a

stormy complicated course. Otitis prone children usually have a backdrop of atopy, craniofacial anomalies, immunodeficiency or adverse environmental factors. Persistent OME usually resolves with time, those children who have significant hearing loss, may need ventilating tubes (grommet). Mild cases of CSOM can be managed with topical quinolones; more serious cases need expert ENT consultation (**Table 3**).

PREVENTION

Primary prevention consists of promoting exclusive breastfeeding for at least 6 months; avoid bottle feeding and pacifier use; vaccination with the Hib and conjugate pneumococcal vaccines; environmental control; strict avoidance of smoke exposure; avoiding crowded areas especially day-care units; optimal management of allergic rhinosinusitis; and maintaining good nutrition.

Prevention of recurrent otitis media has been advised in children who have had three or more documented episodes of otitis media in 6 months, or more than 4 episodes in 12 months. Modalities available for prevention of otitis media include immunoprophylaxis and chemoprophylaxis. Prophylactic antibiotics should be discouraged. These children should be evaluated for craniofacial anomalies, and immune disorders (IgA deficiency, ciliary dyskinesia).

Table 3 Indications for referral to an ENT surgeon

Clinical	Reason for referral	Expected procedure
Acute otitis media	Indeterminate diagnosis; inability to visualize drum Toxic severe AOM Complicated AOM	Cerumen clearance, Confirm diagnosis Myringotomy Co-manage
Persistent OME	Confirming fluid Hearing loss	Tympanometry Audiometry Grommet tube placement
	Adenoidal hypertrophy	Adenoidectomy
Recurrent otitis media	Identification of pathogen Cytology	Myringotomy with aspiration
CSOM	Draining ears	Aural toilet, Surgery

IN A NUTSHELL

1. Antibiotics for AOM are indicated in (1) infants less than 6 months of age with presumed or confirmed diagnosis; (2) those 6 months–2 years with confirmed diagnosis or serious disease; and (iii) more than 2 years with confirmed diagnosis and serious disease.
2. Prescribe an antibiotic which is clinically and microbiologically active against both *S. pneumoniae* and *H. influenzae*. Amoxicillin 40–50 mg/kg/day is the first-line agent.
3. Obvious improvement should start in 72 hours. In case of nonresponse, initiate second line agents which include amoxicillin-clavulanic acid, cefuroxime or ceftriaxone.
4. If pain still does not subside within 48–72 hours and the tympanic membrane is still bulging, surgical treatment (myringotomy) is indicated. Myringotomy refers to a therapeutic incision usually given in anterior lower quadrant of the tympanic membrane.
5. Decongestants and antihistaminics do not shorten the overall duration of illness; these may help symptomatically.

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Chapter 39.7

Approach to a Child with Cough

NK Subramanya, Vidya K

Cough is a frequent presenting symptom seeking medical attention. Cough is an important protective reflex that allows clearance of secretions and particulates from the airways, so as to keep the airway clean and healthy. Cough is not a disease by itself, but, a symptom of underlying disease ranging from benign self-limiting upper respiratory tract infection to severe life-threatening disease. Cough in children causes significant anxiety to parents. Drugs prescribed for treatment of cough and the available over the counter sales account for huge revenue sales and it is important to note that majority of these medications are unnecessary, irrationally prescribed or administered by parents.

Cough is the symptom of respiratory disease which may be secondary to a non-respiratory illness such as a cardiac disease. When cough presents with other symptoms that gives clue to the causative factors like fever, dyspnea, hemoptysis, etc. the diagnosis depends on the clinical manifestations. Any respiratory disease can manifest with cough, thus discussing all the causes of cough is beyond the scope of this chapter. In this chapter, we will focus more on diseases where cough is the *sole manifestation*.

APPLIED ANATOMY AND PHYSIOLOGY

Cough receptors are present in airways, sinuses, middle ear, pleura, diaphragm, but the distribution of receptors is nonuniform. The intensity of cough is maximum when it is laryngeal (vocal cords). The cough becomes less explosive as we move proximal or distal to vocal cords in the airways. Vagal afferent nerves regulate involuntary coughing. There is higher cortical control that regulates voluntary coughing. The implication of cortical regulation is evident from the fact that the placebos can have profound effect on coughing. The psychological issues can be considered either the cause or effect of coughing. Cough center is situated in the medulla oblongata, which will be suppressed by cough suppressants. The defensive nature of the cough reflex can be suboptimal in neuromuscular weakness of muscles of respiration. Violent bouts of cough can cause syncope, rib fractures, subconjunctival hemorrhage, prolapse, hernia and alterations in intracranial pressures. Cough can be categorized based on duration (i.e., acute or chronic), quality (dry or wet, brassy or staccato) or etiology (specific or nonspecific).

ACUTE COUGH

Acute cough is generally defined as the cough of less than 4 weeks duration. The pediatric definition of acute or chronic cough is based on the natural history of acute upper respiratory tract infections (URTI) in children, wherein usually the cough resolves within 1–3 weeks. Hence, it is logical to define chronic cough as daily cough lasting more than 4 weeks. Published definitions of chronic cough in children have varied duration from 3 weeks to 12 weeks. In contrast, the current definition of duration of chronic cough in adults is 8 weeks. The cough between 4 weeks and 12 weeks in adults is called subacute cough, the relevance of this definition in children is not clear. It may be worth mentioning that these cut-offs can sometimes also vary for the purpose of defining a particular disease suspect, e.g., a child with prolonged cough of more than 2 weeks in our country is considered as a TB suspect.

The cause of acute cough in children is usually obvious by clinical evaluation. The infections of upper and lower respiratory tracts account for majority of cases. Nose block, mouth breathing, postnasal discharge, soreness of pharyngeal mucosa exposing cough receptors to be stimulated believed to be responsible for cough.

Postinfectious Cough

The postinfectious cough can follow an upper or lower airway infection. The child continues to cough while other symptom like fever resolve. It is thought to be due to exhaustive inflammation and disruption of airway mucosal integrity. In lower respiratory tract infection this is often associated with excessive accumulation of mucus and transient airway and cough receptor hyper-responsiveness. This may be clinically identified as acute or subacute cough pattern described in adults.

Management of Acute Cough

The diagnosis of the illness causing acute cough is essentially clinical such as acute rhinosinusitis, acute otitis media, sore throat, acute laryngitis, etc. They are managed as per the standard guidelines. The accompanying cough resolves with recovery of underlying cause in most of the children. There is no need of laboratory investigations in general, unless an individual case demands work-up. Anticold preparations available over the counter and also largely prescribed by clinicians have largely been criticized for lack of scientific evidence. The expectorants have variable response and cough suppressants can be dangerous in children younger than 6 years of age. The clinician should weigh the advantages of such prescription over the benign self-limiting nature of many infections in day to day practice. The herbal remedy, honey, and steam inhalation are popular among parents and pediatricians but lack strong scientific evidence.

Recurrence of Acute Cough

Upper respiratory tract infections are common in early life and on an average 6–8 episodes occur in infancy. The frequency of these episodes decrease with increasing age and reassurance to the anxious parents may avoid unnecessary investigations. However, malnutrition, bottle feeding, day care admissions, exposure to environmental factors like parental smoking, pollution is responsible for *recurrent episodes* of acute cough. Exacerbations of asthma as a cause of recurrent cough is common and associated history should be elicited to make the diagnosis.

CHRONIC COUGH

Chronic cough is defined as cough lasting more than 4 weeks. Chronic cough in children is evaluated and managed differently than in adults. Unlike in adults, the relationship between chronic cough and upper airway disorders, asthma, and gastroesophageal reflux disease (GERD) is less convincing in children. Pediatric cough can be classified in several ways, including those based on the etiology, time frame, characteristics, and specific/nonspecific cough.

Cough is categorized as *expected*, *specific* and *nonspecific*. In *expected cough*, the presence of cough is expected (e.g., after an acute respiratory tract infection). In *specific cough*, the etiology and necessity for further investigations is usually evident from the presence of coexisting symptoms or signs (e.g., suppurative lung disease, immunodeficiency, etc.). The presence of any of these symptoms or signs suggests that the cough is likely to be associated with an underlying specific etiology. The clinical evaluation and investigation depend upon the suspected specific diagnosis. The standard guidelines for the diagnosis should be followed,

e.g., work-up of a child with suspicion of tuberculosis. Specific pointers of cough are listed in **Table 1**. The diagnosis can be based on the characteristics of cough such as age at the onset of cough (**Table 2**), nature of cough (**Table 3**), and the timing of the cough in the day (**Table 4**). A detailed history, repeated questions and clinical examination (**Table 5**) are needed to find out etiology.

Some Special Situations with Chronic Cough

Upper Airway Cough Syndrome

Upper airway cough syndrome (UACS), also referred to as post-nasal drip, is characterized by dry cough with throat clearing associated with upper airway problems such as rhinosinusitis of

Table 1 Specific pointers of cough

Asthma	Seasonal, trigger induced, atopic, nocturnal, responding to salbutamol/steroids
Bronchiectasis or recurrent pneumonia	Cystic fibrosis, primary ciliary dyskinesia (PCD), immunodeficiency, congenital airway lesions, foreign body, tracheoesophageal fistula (TEF)
Aspiration	Neurologically abnormal, TEF, GERD, cleft palate
Chronic infections	TB, nontubercular mycobacteria, fungal diseases, parasites
Interstitial lung disease	Drugs, radiation, autoimmune diseases
Airway abnormality	Tracheomalacia, airway compressions
Cardiac diseases	Murmurs, pulmonary hypertension
Miscellaneous pulmonary conditions	Tumors

Table 2 Age and onset of cough

Age	Acute	Recurrent	Persistent
Infancy	Viral infection	GERD	PCD, Congenital anomalies
Early childhood	Foreign body	Asthma	Retained foreign body Tuberculosis
Older children	Asthma	Rhinosinusitis psychogenic	Bronchiectasis (CF/Non-CF/immunodeficiency), ILD

Abbreviations: CF, cystic fibrosis; GERD, gastroesophageal reflux disease; ILD, interstitial lung disease; PCD, primary ciliary dyskinesia.

Table 3 The nature of cough

Nature of cough	Probable cause
Throat clearing	Postnasal drip
Dry, irritating	Postviral
Barking cough	Laryngitis
Brassy	Tracheitis/mediastinal mass or nodes
Paroxysmal	Pertussis, asthma
Staccato cough	Chlamydial infection
Nocturnal	Asthma
Wet, rattling	Suppurative lung diseases

Table 4 Timing of cough

Time of cough	Probable cause
Early morning	Dry cough: Asthma Wet cough: Bronchitis
Worsen in evening	Pollution
Worse in night	Asthma, postnasal drip
After feeds, lying down	GERD
Soon after exercise	Asthma
Loud, bizarre, absent during sleep	Psychogenic

Abbreviation: GERD, gastroesophageal reflux disease.

Table 5 Cough and clinical features

Clinical finding	Cause
Wheeze, atopy, rhinitis	Asthma
Cold, fever, rashes	Viral infections
Excessive regurgitation	GERD
Multiple multifocal infections	Immunodeficiency
Clubbing	Suppurative lung diseases, ILD
Malabsorption, failure to thrive	Cystic fibrosis

Abbreviations: GERD, gastroesophageal reflux disease; ILD, interstitial lung disease.

infective or allergic origin. Some of the children also have GERD as the comorbid condition aggravating the cough.

Aspiration Syndrome

Micro- or macroaspiration of contents of upper gastrointestinal tract (GIT) can occur from lower esophagus (GERD), mid esophagus (tracheoesophageal fistula) or at higher level (palate-pharyngeal in coordination, cleft palate, etc.). The relationship of the cough aggravated by supine posture or after feeds makes the diagnosis clinically possible. Barium studies clinch the diagnosis in tracheoesophageal fistula (TEF) and diaphragmatic hernia. Gastroesophageal reflux disease requires 24-hour pH monitoring of esophagus, and responds to thickening of feeds with antireflux therapy (proton pump inhibitor).

Asthma

Asthma is a clinical diagnosis. Cough in asthma is recurrent, episodic, seasonal, trigger-induced, nocturnal and occasionally paroxysmal resulting in vomiting. The accompanying breathlessness and wheeze help in the diagnosis. Cough responds typically to bronchodilators and steroids. Isolated cough in the absence of wheezing, responding to bronchodilators is called cough variant asthma.

Pertussis

Pertussis is often underdiagnosed. The typical paroxysmal cough with or without whoop, with laboratory evidence of lymphocytosis is hallmark of the disease. The diagnosis should be considered even in immunized children. Cough does not respond to bronchodilators or cough suppressants. Cough is very distressing and macrolides (azithromycin) given early in the first week of illness reduces morbidity.

Tuberculosis

Cough of more than 2 weeks with history of contact in developing country should be evaluated for tuberculosis. Parenchymal

involvement, extrinsic compression of airways by lymph nodes, endobronchial spread, cavitation, and bronchiectasis can cause chronic cough. The attempt should always be made to isolate acid fast bacilli (AFB).

Foreign Body in Airway

In acute cases, history of sudden onset of cough with choking in a toddler should raise the suspicion of foreign body (FB). In chronic cases the ingestion of FB may be *forgotten* and high index of suspicion is needed. When in doubt, rigid bronchoscopy should be done even in the *absence* of history. X-ray chest can show air trapping, localized emphysema, and mediastinal shift depending on the sight of FB in airways. Normal X-ray does not exclude the presence of FB.

Psychogenic Cough

It is also referred to as habit cough typically seen young adolescents and cough is explosive, attention-seeking and disappears in sleep. Counseling and referral to psychiatrist, multidisciplinary approach is required.

Protracted Bacterial Bronchitis

Prolonged *wet* cough of more than 2 weeks duration is usually due to the formation of *biofilms* due to microbial colonization in the airway mucosa making it difficult to treat. Prolonged antibiotics for 4 weeks are needed.

Evaluation and Approach to Chronic Cough

Every effort should be made to arrive at specific diagnosis of cough. If specific diagnosis is not possible at the point of evaluation, a diagnosis of nonspecific cough is made. Nonspecific cough has been defined as usually dry cough in the absence of identifiable respiratory disease or known etiology. The categorization is overlapping and is not very well demarcated. Cough is subjected to period effect (i.e., spontaneous resolution of cough). The therapeutic benefit of placebo treatment for cough has been reported to be as high as 85%. This forms the basis for *wait and watch*, and *review* approach in many children with nonspecific cough. It can also be noted that in some children the specific pointers to diagnosis evolves over a period of time.

Chest X-ray should be done in all cases of chronic cough except in asthma, as asthma is essentially clinical diagnosis. Radiological findings in chronic cough are summarized in **Table 6**. Other investigations are listed in **Table 7**.

A Simplified Approach to Chronic Cough

1. If specific pointers are present, evaluate as per standard guidelines.
2. If not, do chest X-ray and spirometry (if above 6 years, based on the availability).
3. Is cough characteristic? If yes, refer to **Tables 2 to 4**.
4. If not it is nonspecific cough, follow *wait, watch and review*.
5. Evaluate for environment, child's activity and review in 1–2 weeks.
6. If not resolving, discuss with parents for further evaluation.
7. Treatment after evaluation and specific diagnosis is ideal approach. However, few clinicians may try a trial of therapy (antimicrobial therapy for *wet cough* and bronchodilators for *dry cough*).

Table 6 Chest X-ray in chronic cough

Radiological findings	Probable causes
Normal	Asthma, postnasal drip, aspiration syndromes, habit cough, FB, drugs, vascular compression
Persistent shadow	FB, TB, congenital anomalies
Multifocal lesions	Aspiration, asthma, cystic fibrosis, immunodeficiency, congenital heart disease
Focal shadows	Nodes, tumors, cysts
Interstitial pattern	Infections, ILD

Abbreviations: FB, foreign body; ILD, interstitial lung disease; TB, tuberculosis.

Table 7 Investigations in chronic cough

X-ray chest	All cases
Sputum examination	AFB, fungal studies
Barium study	Aspiration syndromes
2D-Echo	CHD, Pulmonary hypertension
Pulmonary function tests	Asthma
HRCT	Suppurative lung disease, interstitial lung disease

Abbreviations: AFB, acid fast bacilli; CHD, congenital heart disease.

IN A NUTSHELL

1. *Acute cough* is commonly due to URTI, self-limiting, and unnecessary investigations and indiscriminate use of drugs should be avoided.
2. *Chronic specific cough* should be evaluated based on clinical clues/pointers, individualized in approach, and treated.
3. *Chronic nonspecific cough* should be evaluated over the period of time; wait and watch. Re-evaluate for appearance of specific pointers; consider trial of antibiotics (infective) or inhaled corticosteroids (allergic). Parents should be involved in decision making.

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Chapter 39.8

Common Cold and Acute Pharyngitis

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Acute respiratory infections (ARIs) are common causes of morbidity and mortality in children and one of the main reasons for visit to pediatric practitioners. A significant chunk of ARIs (80–90%) is contributed by upper respiratory tract infections (URTIs) including common cold (rhinitis), pharyngitis, tonsillitis, sinusitis, and acute otitis media. Majority of URTIs are caused by viruses; bacterial infections are responsible for only a minor fraction. Irrational prescribing of antibiotics is a common practice in URTIs, thus a thorough knowledge of these disorders is essential to avoid unnecessary use of antibiotics and prevent emergence of drug resistance.

COMMON COLD (RHINITIS)

Common cold is a mild, self-limiting viral illness with prominent nasal symptoms (nasal stuffiness, coryza, sneezing). Though, referred to as rhinitis, paranasal sinuses are frequently affected and therefore, viral rhinosinusitis may be a more appropriate terminology.

Etiology

As discussed earlier, common cold is a viral illness. More than 100 different viruses have been described to cause common cold, the most common being rhinovirus responsible for about 40–60% of cases. The major etiological agents are listed in **Box 1**.

BOX 1 Etiological agents of common cold

Most common: Rhinovirus

Common: Coronavirus, metapneumovirus*, respiratory syncytial virus*, influenza virus; and parainfluenza virus*

Occasional: Adenovirus; enterovirus; and bocavirus*^.

*Agents causing symptoms in addition to those of common cold
^ often found as coinfection with other agents.

Epidemiology

Common cold occurs more frequently in rainy season and winters in tropical climate. Usual incubation period is 1–5 days. Young children have more frequent colds (average 6–8 episodes/year), have greater concentration of virus in their secretions and shed virus for longer periods of time. They are also a common source for spreading infection to others, particularly adults. Not surprisingly, therefore, attendance in day care centers and presence of young siblings at home are risk factors for the illness.

Pathophysiology

Transmission of infection occurs by hand contact with infected secretions, small particle aerosol or large particle aerosol. Mode of transmission varies with different agents. Rhinovirus is primarily spread by direct contact with infected secretions. After direct inoculation of nasal mucosa or from conjunctiva via lacrimal duct, virus reaches the nasopharynx and enters the epithelial cells via cell surface receptors and starts replicating leading to acute inflammatory response. Degree of epithelial destruction and cytopathology vary with different viral agents. Little or no epithelial damage occurs in rhinoviral infection. Increased vascular

permeability and vasodilatation cause symptoms of rhinorrhea and nasal obstruction. Sneezing and increased mucus secretion occurs due to cholinergic stimulation. Nasal discharge may become mucopurulent between day 2 and 7 of illness because of desquamated epithelial cells and polymorphonuclear leukocytes. Eustachian tube dysfunction and involvement of paranasal sinuses occur frequently because of spread of inflammation to eustachian tube and sinus ostium, predisposing to development of otitis media and bacterial sinusitis. Viremia usually does not occur during typical common cold, infection being restricted to epithelia of upper respiratory tract. Impairment of mucociliary clearance may persist for 3–4 weeks.

Clinical Features

Symptoms of common cold are not specific for any etiological agent. The illness usually starts with dryness and irritation in nose and a scratchy throat. Nasal stuffiness, sneezing, watery nasal discharge, watering eyes and cough follow. There may be low-grade fever, muscle aches and malaise. Nasal secretions may become thick and mucopurulent during the course of illness. However, that does not signify bacterial superinfection. Examination may reveal congested, erythematous nasal turbinates, rhinorrhea and nasal excoriation. Infants are more likely to have fever and nasal obstruction which may cause faster respiration and feeding difficulty. Usual duration of symptoms is 7 days but symptoms may persist for up to 2 weeks in few.

Differential Diagnosis

Allergic Rhinitis

Allergic rhinitis should be distinguished from infectious rhinitis in a child with recurrent colds. Nasal discharge is clear and watery in allergic rhinitis with a pale and boggy appearing nasal mucosa. Presence of nasal/ocular pruritis, positive family and/or personal history of allergic disorders, possible allergic triggers, nasal eosinophilia and serum IgE help in diagnosing allergic rhinitis.

Sinusitis

Headache/facial pain, anosmia, persistence of nasal discharge and cough for more than 2 weeks in an illness which started as usual common cold should lead to the suspicion of sinusitis.

Initial symptoms of some illnesses, e.g., pertussis, diphtheria, measles, epiglottitis are similar to common cold but over the course of illness other features become apparent.

Management

Common cold is a mild, self-limiting illness and no therapy is indicated in majority of cases. Antibacterial and antiviral agents are of no benefit. Antibiotic use is potentially harmful as it increases emergence of resistant organisms. Use of symptomatic treatment in children is not proven. Few of these options are discussed here:

Antipyretic and Analgesics

Acetaminophen can be given for symptomatic relief of fever and aches.

Cough and Cold Medications

Various over the counter (OTC) cough and cold medications containing varying combination of antihistaminics, antitussives, decongestants, mucolytics and expectorants are available in the market. First generation antihistaminics have been shown to reduce rhinorrhea in adults with colds due to their anticholinergic action. However, no studies are reported in children. Similarly, no robust studies or meta-analysis support any role of cough suppressants, expectorants, or decongestants in the management

of common cold for symptomatic relief. Systemic decongestants (pseudoephedrine, phenylephrine) may cause serious side effects (CNS stimulation, tachycardia, and hypertension). Mucolytics are also not effective in children.

Relief of Nasal Obstruction

Efficacy of nasal decongestants (xylometazoline, oxymetazoline) in children with common cold is unproved and potential side effects are a concern especially in young children. Excessive use of nasal vasoconstrictors may cause rebound nasal obstruction. They are not approved for children less than 2 years of age. Use of isotonic saline nasal drops and gentle aspiration may provide temporary relief of nasal obstruction in young children. General humidification of room air may dilute tenacious secretions and facilitate their elimination. However, a Cochrane review concluded that steam inhalation does not offer consistent benefit.

Micronutrients

A major controversy relates to efficacy of vitamin C in prophylaxis and treatment of common cold. A Cochrane review concluded that prophylactic vitamin C does not reduce the incidence of cold but there is a small benefit on duration and severity of cold. Given at the onset of cold, it does not have any benefit. Another recent Cochrane review concluded that zinc, administered within 24 hours of onset of symptoms, shortened the duration and severity of cold in healthy people and prophylactic use reduced the incidence of colds and decreased school absenteeism in children. However, in view of differences in study population, dosages, formulations and duration of treatment used in different studies and potential side effects of zinc lozenges, no firm recommendations about the dose, duration and formulations could be made.

Prognosis and Complications

Common cold is a self-resolving condition with complete recovery in 7–10 days. Complications occur in a minority of children and include otitis media, sinusitis, adenoiditis, lower respiratory tract infections and exacerbations of bronchial asthma.

PHARYNGITIS

Pharyngitis is inflammation of the mucous membrane and underlying structures of pharynx causing sore throat and accompanied by objective evidence of inflammation (erythma, exudates or ulceration). It is subdivided into (a) *nasopharyngitis*—sore throat accompanied by nasal symptoms and almost always viral in origin; and (b) *tonsillopharyngitis*—sore throat without nasal symptoms and can be caused by wide variety of agents including bacterial, viral and fungal. Majority of pharyngitis cases are self-limiting viral illnesses. Group A β hemolytic *Streptococcus* (GAS) or *Streptococcus pyogenes* is the most important bacterial cause of pharyngitis because of its potential to cause acute rheumatic fever. Prevention of acute rheumatic fever by adequate and timely treatment of GAS pharyngitis defines the management of pharyngitis.

Epidemiology

Children of any age can develop pharyngitis. However, pharyngitis due to *S. pyogenes* occurs primarily in children between 5 years and 15 years of age and is unusual in children below 3 years of age. Pharyngitis occurs more frequently during colder months of the year. Incubation period varies between 2 days and 5 days. Children are major reservoir of infection. In India, prevalence of GAS pharyngitis ranges from 4.2% to 13.7% with incidence rates varying between 0.12 and 0.95 episodes per child per year. Various studies have shown asymptomatic streptococcal throat carriage rate between 2.3% and 20%.

Etiology

Most cases of pharyngitis in children are viral. *S. pyogenes* is the most important bacterial cause and accounts for 15–30% cases. Adenovirus is the most common cause of nasopharyngitis, other common viral agents being influenza and parainfluenza. Although rhinovirus, respiratory syncytial virus, corona virus, human metapneumovirus and bocavirus infection are common in children, objective evidence of pharyngeal inflammation is less common. In enteroviral infection, pharyngeal involvement is often overshadowed by systemic complaints (fever, exanthema, meningitis). Epstein-Barr (EBV) virus can cause pharyngitis as part of infectious mononucleosis. Primary and recurrent herpes simplex virus (HSV) infection, occasionally, have pharyngeal involvement. Bacteria other than GAS are rare causes of pharyngitis and include group C and G *Streptococcus*, *Haemophilus influenzae* and *Neisseria meningitidis* (along with systemic illness), *Arcanobacterium haemolyticum* and *Corynebacterium*. *Chlamydia pneumoniae* and *Mycoplasma* have also been implicated as cause of acute pharyngitis. Exudative pharyngeal involvement with *Candida* can occur in children who are immunocompromised and whose normal throat flora have been disrupted. **Table 1** enlists etiological agents of pharyngitis.

Clinical Features

The onset of pharyngitis is usually with fever, sore throat and anorexia. Examination shows objective evidence of pharyngeal inflammation in the form of pharyngeal erythma, exudates or ulceration. Clinical distinction between GAS pharyngitis and viral pharyngitis cannot be absolute as there is considerable overlap in clinical features. However, presence of rhinorrhea, cough, hoarseness, conjunctivitis, diarrhea, exanthema suggest viral etiology. On the other hand, GAS pharyngitis classically presents with sudden onset of sore throat, dysphagia and fever while examination findings include tonsillopharyngeal erythema with or without exudates, tender anterior cervical lymphadenopathy, palatal petechiae, and red swollen uvula, but none of these signs is specific as they can be present in adenovirus and EBV infection too. Also many patients with GAS pharyngitis present with milder

Table 1 Etiological agents of pharyngitis

Common viral causes	Less common viral causes
Adenovirus	Cytomegalovirus
Coronavirus	Herpes simplex virus
Enteroviruses	Reovirus
Epstein-Barr virus	Rhinovirus
Influenza virus A and B	Rotavirus
Parainfluenza virus	Rubella virus
Respiratory syncytial virus	
Common bacterial causes	Uncommon bacterial causes
<i>Streptococcus pyogenes</i>	<i>Actinomyces</i>
	Mixed anaerobes
	<i>Arcanobacterium haemolyticum</i>
	<i>Corynebacterium</i>
	<i>Francisella tularensis</i>
	<i>Haemophilus influenzae</i>
	<i>Legionella</i>
	<i>Leptospira</i>
	<i>Neisseria gonorrhoeae</i>
	<i>Neisseria meningitidis</i>
	Streptococci C and G
	<i>Streptococcus pneumoniae</i>
Other organisms	
<i>Candida</i>	<i>Coxiella burnetii</i>
<i>Chlamydia pneumoniae</i>	<i>Mycoplasma pneumoniae</i>

and less classical presentation. Absence of pharyngeal exudates, tender lymphadenopathy, and throat pain have a high negative predictive value for GAS pharyngitis. **Box 2** enumerates features suggestive of viral and GAS pharyngitis.

BOX 2 Clinical features differentiating Group A streptococcal from viral etiology of pharyngitis

Features suggesting group A streptococcal etiology

Sudden onset, absence of cough, tender cervical lymph nodes, palatal petechiae, fever > 38°C, and tonsillar or pharyngeal exudates

Features suggesting viral etiology

Coryza, conjunctivitis, hoarseness, viral exanthema, viral enanthem, diarrhea.

Adenoviral pharyngitis typically presents with fever, pharyngeal congestion, tonsillar enlargement with exudates and enlarged cervical lymph nodes. There may be associated conjunctivitis (pharyngoconjunctival fever). Pharyngeal involvement is overshadowed by other respiratory symptoms (cough, coryza) in influenza and parainfluenza infection. In enteroviral pharyngitis (coxsackie virus, and newer enteroviruses), pharyngeal congestion is present but tonsillar exudates and cervical lymphadenopathy is uncommon. Systemic signs (fever, exanthema, meningitis) are prominent. Herpangina, caused by coxsackie virus A/B and echovirus, presents with fever and painful, discrete gray-white papulovesicular lesions on an erythematous base (which may ulcerate) in posterior oropharynx. In hand-foot-mouth disease, caused by coxsackie virus A 16, painful vesicles and ulcers throughout the oropharynx are associated with vesicles on palms and soles.

Primary and recurrent HSV infection, occasionally have pharyngeal involvement, but the hallmark herpetic lesions are present around the mouth and at mucocutaneous border. EBV pharyngitis can cause a clinical picture of exudative pharyngitis, almost identical to GAS pharyngitis.

Pharyngitis caused by group C and G streptococci and *A. haemolyticum* closely resembles GAS pharyngitis. Pharyngeal diphtheria presents with grayish-white membrane over one or both tonsils which may extend to involve uvula, soft palate and other surrounding areas.

Diagnosis

As bacteria other than *S. pyogenes* are rare cause of pharyngitis and sequelae of acute rheumatic fever do not occur, diagnostic armamentarium is directed towards diagnosis of GAS pharyngitis.

Throat Swab

Culture of throat swab specimen on sheep blood agar is gold standard for diagnosis of GAS pharyngitis. Cultures that are negative at 24 hours should be re-examined at 48 hours after incubation. Performed adequately (swabbing surfaces of both tonsils and posterior pharyngeal wall without touching other oropharyngeal areas), it has sensitivity of 90–95% for diagnosis of GAS pharyngitis. However, the culture isolates have to be seen in the clinical context as many a time the isolate may just be colonizing the throat rather than be a true pathogen.

Rapid Antigen Detection Test

To obviate the problem of delayed diagnosis by throat swab cultures, rapid antigen detection tests (RADTs) have been developed which enable identification of GAS pharyngitis from throat swab specimen within minutes. Older RADT employed latex agglutination and had lower sensitivity of about 70%. Newer tests employ enzyme immunoassay, optical immunoassay and DNA

probes and have sensitivity between 80% and 90%. Specificity of all RADTs is about 95%.

Neither culture nor RADTs differentiate asymptomatic streptococcal throat carriage from bonafide GAS pharyngitis. There is no role for serological test for diagnosis of acute GAS pharyngitis as they indicate past infection.

These diagnostic tests need not be performed in patients with pharyngitis whose clinical and epidemiological features do not suggest GAS pharyngitis, e.g., those with prominent nasal symptoms, herpangina or pharyngoconjunctival fever. Doing so, increases the yield of positive test results and helps in identification of truly infected cases rather than mere GAS carriers. Various clinical scoring systems have been developed to predict the probability of GAS pharyngitis and selectively use throat culture/RADT in those with high-risk of GAS infection. Clinical sign and symptoms used in these scoring systems include absence of cough, enlarged tender cervical lymph nodes, tonsillar exudates/swelling, age, fever above 38°C. Indian Academy of Pediatrics (IAP) has also endorsed the use of throat culture/RADT in the management algorithm of pharyngitis. **Flow chart 1** shows the IAP management algorithm for pharyngitis.

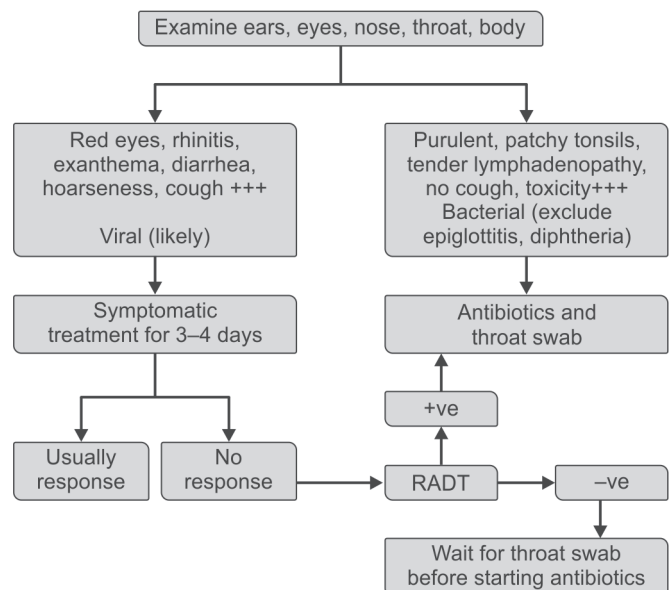
Treatment

As majority of pharyngitis cases are viral, symptomatic treatment is all that is required. Acetaminophen can be given for fever and pain relief. Aspirin should be avoided because of risk of Reye's syndrome in children. Warm saline gargles can be advised in older children. Simple lemon/ginger/honey based lozenges may be soothing, but those containing potentially harmful substances should be avoided.

Antibiotics should not be given to a child with pharyngitis in the absence of diagnosed GAS infection. The main goal of antibiotic treatment is prevention of complications of streptococcal disease as otherwise GAS pharyngitis is a self-limiting condition. Acute rheumatic fever can be prevented if antibiotics are started up to 9 days after onset of illness.

Penicillin is the treatment of choice in view of narrow spectrum of activity, low cost and high efficacy. Amoxicillin is usually preferred over penicillin V in children because of better acceptability and availability of pediatric formulations.

Flow chart 1 IAP management algorithm for pharyngitis



Abbreviation: RADT, rapid antigen detection tests.

For penicillin allergic individuals, macrolides (erythromycin/clarithromycin/azithromycin) are effective but they should not be used as first line antibiotics in nonallergic individuals. No strain of GAS has shown resistance to penicillin till date; however widespread macrolide resistance has been reported. First generation cephalosporins can also be used in penicillin allergic individuals who do not exhibit immediate hypersensitivity. Many studies have suggested that cephalosporins are more effective than penicillin in GAS eradication. However, they are expensive and because of wide spectrum of activity can encourage the development of resistance over a broad range of bacterial pathogens.

Most antibiotics need to be given for 10 days to achieve pharyngeal eradication of GAS, however 5 day course of azithromycin has been shown to be effective. Some preliminary studies have shown that once daily amoxicillin therapy is effective in treatment of pharyngitis.

Table 2 summarizes the antibiotic options and dosage for GAS pharyngitis.

Prognosis and Complications

Pharyngitis is a self-limiting condition that resolves spontaneously in 4–10 days. However complications, both suppurative and nonsuppurative, can occur in GAS infection (**Table 3**).

IN A NUTSHELL

1. Common cold is a viral illness, and antibiotics are not required.
2. Nasal discharge can become mucopurulent during course of common cold and is not an indicator of secondary bacterial infection.
3. Common cough and cold medications are not effective in children.
4. Clinical distinction between viral and bacterial etiologies of pharyngitis is difficult.
5. Throat swab culture and RADT are recommended if there is clinical suspicion of GAS pharyngitis.
6. Penicillin is first line treatment of GAS pharyngitis.
7. Antibiotics given within 9 days of onset of symptoms can prevent acute rheumatic fever.

Table 3 Complications of group A β hemolytic *Streptococcus pharyngitis*

Suppurative complications	Nonsuppurative complications
<ul style="list-style-type: none"> • Bacteremia • Peritonsillar/retropharyngeal abscess • Pneumonia • Otitis media • Sinusitis • Mastoiditis • Cervical lymphadenitis 	<ul style="list-style-type: none"> • Rheumatic fever • Poststreptococcal glomerulonephritis • Reactive arthritis • Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS)

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Table 2 Therapeutic options for group A streptococcal pharyngitis

Drug	Dose	Duration
<i>Penicillins</i>		
Penicillin V	Children < 27 kg: 250 mg BD/TDS Children > 27 kg: 500 mg BD/TDS	10 days
Amoxicillin	40 mg/kg/day TDS	10 days
Benzathine penicillin	Children < 27 kg: 600,000 U Children > 27 kg: 1200,000 U	Once
<i>For Penicillin allergic individuals</i>		
First generation cephalosporin		
Cephalexin	25–50 mg/kg/day BD-QID	10 days
Cefadroxil	30 mg/kg/day BD	
Erythromycin ethylsuccinate	40–50 mg/kg/day BD/TDS	10 days
Erythromycin estolate	20–40 mg/kg/day BD/TDS	10 days
Clarithromycin	15 mg/kg divided BD (max 250 mg BD)	10 days
Azithromycin	12 mg/kg OD (max 500 mg)	5 days

Chapter 39.9

Sinusitis

SD Subba Rao

Sinusitis in most children coexists with rhinitis; hence the term *rhinosinusitis* was coined by 1997 Task Force of Rhinology and Paranasal Sinus Committee. Acute rhinosinusitis (ARS) results from infection of one or more of the paranasal sinuses. Rhinosinusitis is a widely prevalent disease affecting more than 14% of adults and children. A viral infection associated with the common cold is the most frequent etiology of ARS (**Box 1**). A small percentage of post-viral ARS get transformed into acute bacterial rhinosinusitis (ABRS) (**Fig. 1**). It has high propensity to become chronic. Though the acute form of rhinosinusitis is unimicrobial, multiple microorganisms characterize the chronic form. In the chronic form, microbes usually demonstrate antimicrobial resistance and pose a therapeutic challenge for the clinician. Early detection and prompt and appropriate treatment of rhinosinusitis could possibly avert chronic rhinosinusitis.

DEVELOPMENT AND ANATOMY OF PARANASAL SINUSES

The paranasal sinuses develop as outpouching of the nasal cavity. The onset and duration of development of the paranasal sinuses vary depending upon the location. Development of the paranasal sinuses may not be fully complete until 20 years of age; however, by 12 years of age, the nasal cavity and paranasal sinuses in most individuals have nearly reached adult proportions.

- The maxillary sinuses are present at birth and expand rapidly by 4 years of age.
- The ethmoid sinuses are comprised of a collection of tiny air cells and are present at birth; each of these tiny air cells have their own opening into the nose.
- The sphenoid sinuses begin to develop by 2 years of life. They get pneumatized by 5 years of life and attain the adult size by 12 years.
- Frontal sinus development is variable:
 - Radiographic differentiation of frontal sinus from ethmoid sinus happens by 6–8 years of age.
 - Frontal sinuses complete their development by 8–10 years of age.
 - Majority of individuals (80%) have bilateral frontal sinuses and about 20% have unilateral hypoplasia of the frontal sinus.

DEFINITIONS

Sinusitis is defined as inflammation of the mucosal lining of one or more of the paranasal sinuses. Two or more of the following findings clinically define sinusitis:

- Nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip); \pm facial pain/pressure; and \pm cough *and either*
- Rhinoscopic signs suggestive of nasal polyps/mucopurulent discharge from middle meatus/edema or mucosal obstruction; *and/or*
- *CT changes*: Findings suggestive of mucosal changes in the ostiomeatal complexes or sinuses.

This definition, however, is not pragmatic as routine use of CT is not advised. Sinusitis is ultimately a clinical diagnosis (**Box 2**).

BOX 1 Common organisms causing acute rhinosinusitis

Viruses

- Rhinoviruses, coronavirus, influenza viruses, parainfluenza viruses, adenovirus, respiratory syncytial virus (RSV), and enterovirus

Bacteria

- *Streptococcus pneumoniae*
- *Haemophilus influenzae*
- *Moraxella catarrhalis*
- Beta-hemolytic *Streptococcus pyogenes*
- *Mycoplasma* and chlamydial species.

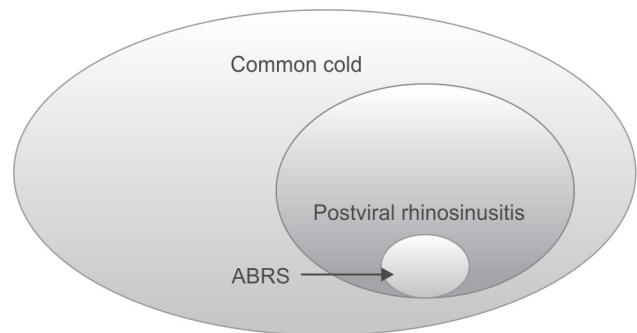


Figure 1 Relation of common cold, acute rhinosinusitis (ARS) and acute bacterial rhinosinusitis (ABRS)

BOX 2 Definitions of sinusitis

- When the duration of symptoms is less than 10 days then it is referred to as *acute viral rhinosinusitis*.
- When the symptoms increase after 5 days or persist beyond 10 days then it is referred to as *acute postviral rhinosinusitis*.
- When there is secondary bacterial infection of the sinuses then the term *acute bacterial rhinosinusitis* is used.

Acute Bacterial Rhinosinusitis

It is characterized by the presence of at least 3 of the following signs/symptoms:

- Pain locally which again could be unilateral
- Purulent secretion in cavum nasi, which may be unilateral
- Fever above 38°C
- Increased erythrocyte sedimentation rate/C-reactive protein (ESR/CRP)
- Deterioration after an initial milder phase of illness.

Acute bacterial rhinosinusitis has been classified as *acute*, *subacute*—symptoms completely resolve within or more than 30 and less than 90 days; and *recurrent acute*—at least three episodes of less than 30 days duration separated by intervals of more than or equal to 10 days without symptoms in a 6-month period, or at least four such episodes in a 12-month period.

Chronic Rhinosinusitis

Chronic sinusitis is defined by episodes of inflammation of the paranasal sinuses that last for above 90 days, during which patients have persistent symptoms.

PREDISPOSING FACTORS

- *Environmental exposures*: Seasonal variations, dust, dampness, exposure to other children with acute respiratory infections, air

pollution with exposure to air pollution, mucosal irritants (e.g., dry air, chlorinated water) have all been associated with an increase in the prevalence of symptoms of ARS.

- **Anatomical factors:** This could include—septal deviation, choanal atresia, nasal polyps and hypoplasia of sinuses.
- **Allergy:** Literature is not clear about the role of allergy in predisposing to ARS.
- **Ciliary impairment:** Loss of cilia and ciliated cells leading to impaired mucociliary clearance in allergic rhinitis predisposes to ARS. This has been seen in both viral and bacterial rhinosinusitis. Ciliary function is also disrupted in smokers and individuals with allergy thus making them prone to acute sinusitis.
- **Smoking:** Smokers with allergic inflammation have an increased susceptibility to ARS.
- **Concomitant chronic disease:** Some chronic diseases like bronchitis, asthma, diabetes mellitus, cardiac disease, and malignancy increase predisposition to ARS.
- **Sudden changes in atmospheric pressure** (e.g., descent in an airplane).

PATHOGENESIS

The paranasal sinuses are usually sterile, but the membranes that line the nose are continuous with the membranes that line the sinus cavities. Therefore, the paranasal sinuses may be contaminated with bacteria that colonize the nasal mucosa and nasopharynx. The contaminating bacteria are typically removed by mucociliary clearance. When mucociliary clearance is altered (e.g., by conditions that damage the ciliary epithelium or affect the number or function of cilia, the production or viscosity of mucous, or the patency of the Ostia), the sinuses may be inoculated with large numbers of microorganisms, and infection may develop.

The integrity of the ostiomeatal complex is most crucial for sinus health. Ostial obstruction is usually the start point for sinusitis. It generates a negative pressure in the sinus, which leads to fluid seepage into the sinus. This fluid being a good culture media gets easily infected. This damages the lining cilia, and mucus production is increased. Mucociliary clearance thus gets compromised. A self-perpetuating cycle is established, which needs to be interrupted for optimal outcome. One or more sinuses may be involved with infection.

CLINICAL FEATURES

Acute Bacterial Rhinosinusitis

The clinical and radiographic manifestations of ABRS in children are similar to those of viral upper respiratory infection (URI). The clinical course, particularly the persistence and severity of symptoms, helps to differentiate between uncomplicated viral URI and ABRS.

Typically two types of settings or clinical presentations are seen. Commonly it presents as an illness starting as a viral URI that lasts for 5–6 days and persists beyond or was initially improving but develops worsening symptoms or signs characterized by the new onset of fever, headache, or increase in nasal discharge. It can also present as an acute illness with severe symptoms or signs of high fever 39°C (102°F), purulent nasal discharge or facial pain lasting for at least 3–4 consecutive days right at the beginning of illness.

Cough (wet or dry) is an important symptom in ABRS. The cough must be present during the day, but is often described as worse at night. Nocturnal cough as a single persistent symptom is nonspecific, and more suggestive of postnasal drip or reactive airways disease. The cough becomes more prominent with increasing duration of illness. Nasal symptoms of ABRS include anterior or postnasal discharge, obstruction, and/or congestion.

The nasal discharge may be of any quality: watery, serous, or purulent. Postnasal discharge may cause vomiting.

On examination, there may be mild erythema and swelling of the nasal turbinates with mucopurulent anterior nasal discharge. Drainage from the posterior ethmoids may lead to purulent material in the posterior pharynx. Temperature above or equal to 39°C for at least 3 consecutive days is a component of the severe presentation of ABRS. Sinus tenderness (rare in young children) may be elicited with percussion of the upper molars or percussion or application of direct pressure over the body of the frontal or maxillary sinuses.

Acute bacterial rhinosinusitis needs to be differentiated from allergic rhinitis, infected nasal foreign body, structural abnormalities, and pertussis, particularly in the catarrhal stage.

Complications

These include preseptal (periorbital) and orbital cellulitis, septic cavernous sinus thrombosis, meningitis, osteomyelitis of the frontal bone, and epidural, subdural, or brain abscess.

Chronic Rhinosinusitis (CRS)

Chronic rhinosinusitis is usually a consequence of untreated, improperly treated, or nonresponding ARS. With chronicity, polymicrobes supercede. These include staphylococci, alpha-hemolytic streptococci, anaerobes such as peptostreptococci, *Bacteroides* and *Fusobacterium* species, *Pseudomonas*, other gram-negative enteric bacteria, and fungi.

Chronic rhinosinusitis is predominantly a heterogeneous inflammatory disease. It is multifactorial with environmental and host general and anatomic factors all playing a role in its development. Persistence of infection (biofilms and osteitis), allergy, immunologic disorders, upper airway intrinsic factors, superantigens-induced polyclonal immune response, fungi with eosinophilic inflammation, remodeling, and metabolic problems such as aspirin sensitivity all contribute to the varied picture of chronic rhinosinusitis. It is a tough disease to manage and is characterized by multiple recurrences.

DIAGNOSIS

Diagnosis of rhinosinusitis in children should be suspected when cold does not improve beyond 10 days or nasal stuffiness is present with purulent discharge, facial pain, headache, fever, and diminution/loss of sense of smell. Sneezing and nasal itching are common with allergic rhinitis. In these children with isolated allergic rhinitis, purulent nasal discharge is usually not seen. In those children of allergic rhinitis with superadded sinusitis, the picture is altered, and along with nasal itching and sneezing, purulent nasal secretions and loss of olfaction sense may also be associated.

The diagnosis of uncomplicated ABRS in children is usually made clinically. *Transillumination of sinuses* is useful in hands of experienced person. A flashlight is placed against the patient's cheek and the doctor looks into the patient's open mouth. A lit-up reddened area is seen in the palatal area with normal sinuses. When sinuses are fluid-filled, this reddened area will not be visualized.

Imaging studies are recommended for children suspected to have orbital and intracranial complications of ABRS. Plain radiography of paranasal sinuses has a limited diagnostic role. It is recommended that children with potential orbital or intracranial complications of ABRS undergo contrast-enhanced computed tomography (CT) imaging of the orbits, sinuses, and brain. MRI is indicated for detection of intracranial complications without exposure to radiation.

Microbiologic Studies

Microbiologic studies usually are not necessary for children with uncomplicated ABRS who improve as expected with antimicrobial therapy. However, attempts should be made to identify the pathogen in children who are toxic-appearing, and those with orbital or intracranial complications, immunocompromised children, children with recurrent ABRS, and children who fail to respond to antimicrobial therapy.

MANAGEMENT

Conservative Therapy

Since majority of ARS is viral in origin, they resolve without the need for antibiotics. They need symptomatic treatment in the form of steam inhalation, adequate hydration, instillation of topical decongestants, warm facial packs application, and saline nasal drops and reassurance.

Antibiotics

Antibiotic therapy should be reserved for patients with severe or persistent ARS. Benefits and adverse effects of antibiotics should be carefully weighed before prescribing them. A *wait-and-watch* policy for 7–10 days is fruitful and cost-effective. About 90% recover without antibiotics in a week. Choice of antibiotics should be guided by local susceptibility studies, safety profile, and child's age. Usual preferred are amoxicillin, co-amoxyclov, oral cephalosporins, and macrolide group of antibiotics. A 2 weeks course is usually required.

Other Treatment Modalities

Intranasal corticosteroids either as monotherapy or in conjunction with antibiotics have been shown to be beneficial in treatment of ARS, in a few studies. Nasal saline irrigations and topical cromolyn have also been found to be useful. Ipratropium bromide may be effective in ameliorating rhinorrhea.

The saline irrigations assist to mechanically clear secretions, minimize bacterial and allergen burden, and improve mucociliary function. Antihistamines are useful only when there is coexisting allergic rhinitis. Nasal decongestants are useful to decrease congestion and in the hope of improving better sinus ventilation and drainage. They also provide symptomatic relief of nasal congestion. Nasal decongestants decrease mucus production and can be safely used for 5–7 days. Even though it is routine practice to use steam inhalation for ARS it has not shown any consistent benefits in the treatment of common cold symptoms.

IN A NUTSHELL

1. A viral infection associated with the common cold is the most frequent etiology of ARS. A small percentage of postviral ARS gets transformed into ABRS.
2. Viral URI and allergic rhinitis are the most frequent predisposing factors for ABRS in children.
3. The clinical features of ABRS include cough, nasal symptoms, fever, headache, facial pain and swelling, sore throat, and halitosis.
4. The clinical course, particularly the persistence and severity of symptoms, helps to differentiate between the ABRS and viral URI.
5. The diagnosis of uncomplicated ABRS can be made clinically. There is no role for X-ray, CT or MRI in uncomplicated cases.
6. Treatment is symptomatic. Antibiotics are needed in a small proportion of children with severe or persistent ABRS.

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Chapter 39.10

Tonsils and Adenoids

Pallab Chatterjee

The past decade has seen a major change in the management of adenotonsillar diseases in children. Adenotonsillectomy is now one of the most common surgical procedures in children under 15 years. In recent years, sleep-disordered breathing/obstructive sleep apnea (SDB/OSA) in children (Chapter 39.11) has emerged as the primary indication for removal of the tonsils and adenoids.

ANATOMY

The ring of lymphoid tissue surrounding the opening of the oral and nasal cavities into the pharynx is known as the Waldeyer ring. It is the body's first line of defense against pathogens that are ingested or inhaled. It consists of the palatine tonsils, the adenoids, the lymphoid tissue around the opening of the eustachian tube in the nasopharynx, the lingual tonsil at the base of the tongue, and some scattered lymphoid tissue in the pharynx, especially behind the posterior pharyngeal pillars and along the posterior pharyngeal wall.

The palatine tonsil is situated at the junction of the oral cavity and the oropharynx. The arterial supply is by the tonsillar branches of the dorsal lingual artery and the facial artery, and the venous drainage is into the internal jugular vein. The lymphatic drainage is to the upper deep cervical nodes (tonsillar or jugulodigastric nodes) situated behind the angle of the mandible.

The nasopharyngeal tonsil, or adenoid, is a mass of lymphoid tissue located with the base toward the roof and posterior wall of the nasopharynx and the apex directed towards the nasal septum. Adenoids are fully developed during the seventh month of gestation and continue to grow till the fifth year of life. It is lined by respiratory epithelium (stratified and pseudostratified ciliated columnar), with no surrounding capsule, and simple crypts. The lymphatic drainage is to the lymph nodes situated in the retropharyngeal and pharyngomaxillary space.

IMMUNOLOGY

The adenoids and tonsils serve as secondary lymphoid organs initiating an immune response against antigens entering the body through the nose and the mouth. Both contain B-cell lymphocytes (50–65%), T-cell lymphocytes (40%) and mature plasma cells (3%). They are involved in inducing secretory immunity and regulating secretory immunoglobulin production. The lymphoid follicles thus stimulated result in expansion of B-cell clones and differentiation of B-cells into memory cells and plasma cells. The adenoids and tonsils are thus a source of B-cells for effector sites in the upper respiratory tract mucosa and an important source of secretory immunoglobulin (IgA). The tonsils are immunologically most active between 3 years and 10 years of age, and then decrease after puberty. There are conflicting studies regarding the effects of adenotonsillectomy on immunity, and no studies indicate a demonstrable clinical impact on the immune system.

CLINICAL PRESENTATION

Diseases of the adenoids and tonsils can be broadly classified as those caused by infections or hypertrophy resulting in obstruction of the airways. These disease processes can affect the nasopharyngeal tonsils (or adenoids) or the palatine tonsils, or both. A generalized inflammation of the pharyngeal structures, including tonsils, is known as pharyngotonsillitis. It may be classified according

to the duration of symptoms into acute, chronic and subacute, an acute presentation being the most common. Adenoiditis, an inflammation of the adenoids, is difficult to diagnose in the primary care setting as the tissue is not directly visualized.

ACUTE TONSILLITIS

The most common presentation of acute inflammation of the tonsils is sore throat and fever. It may be associated with enlarged and tender cervical lymph nodes. On examination, the tonsils appear erythematous and swollen with purulent exudates either on the surface or within the tonsillar crypts. There may also be petechiae on the palate, more commonly with Group A beta-hemolytic streptococci (GABHS). There is considerable overlap between the presenting features of a bacterial and a viral tonsillar infection, thus making a definite diagnosis based on clinical examination alone difficult.

The causative organisms for acute pharyngotonsillitis (**Box 1**) are varied with Group A beta-hemolytic *Streptococcus*, adenovirus, Epstein-Barr virus, and *Mycoplasma* accounting for more than 90%. This has been discussed in detail in Chapter 39.8.

Viral Tonsillitis

Adenovirus infection of the tonsils is the most common cause of sore throat in infants and children. It may be associated with high fever, leukocytosis and elevated CRP, creating difficult differential diagnostic problems from bacterial tonsillitis. Coxsackie A viruses cause sporadic outbreaks of herpangina, commonly affecting children between 3 years and 10 years of age. This is a contagious disease that is characterized by small painful vesicular lesions in the oropharynx and on the surface of the tonsils after a 3–4 day incubation period and runs a self-limiting course for 4–5 days. Viral tonsillitis is commonly self-limiting and there are no sensitive rapid diagnostic tests for confirmation of an adenovirus or a coxsackievirus infection. Treatment is symptomatic with avoidance of use of antibiotics.

BOX 1 Causes of pharyngotonsillitis

- A. Common bacterial pathogens
 1. Group A streptococci
 2. Group C streptococci
 3. Group G streptococci
- B. Less common bacterial pathogens
 1. *Chlamydia pneumoniae*
 2. *Mycoplasma pneumoniae*
 3. *Arcanobacterium haemolyticum*
 4. *Corynebacterium diphtheriae*
 5. *Fusobacterium necrophorum*
 6. *Neisseria gonorrhoeae*
 7. *Treponema pallidum*
 8. *Francisella tularensis*
- C. Viruses
 1. Rhinovirus
 2. Adenovirus
 3. Influenza A and B
 4. Parainfluenza
 5. Coxsackievirus
 6. Echovirus
 7. Epstein-Barr virus
 8. Human immunodeficiency virus
 9. Cytomegalovirus
 10. Respiratory syncytial virus
 11. Metapneumovirus
- D. Fungi
 - Candida* species
- E. Parasites
 - Toxoplasma gondii*

Infectious mononucleosis, caused by infection by Epstein-Barr virus (EBV), is an acute self-limiting disease that may present with tonsillitis. Cytomegalovirus infection is also known to produce a syndrome similar to infectious mononucleosis. It may present with hypertrophied tonsils with exudates as those in Group A beta-hemolytic streptococcal infection. The presence of palatal petechiae, splenomegaly and posterior cervical adenopathy are highly suggestive of infectious mononucleosis, while the absence of cervical lymphadenopathy and malaise make the diagnosis much less likely.

Other Organisms

The role of anaerobic bacteria causing tonsillitis in children has been underestimated, and is more common in recurrent or chronic tonsillitis, examples being Vincent's angina and infection with *Fusobacterium necrophorum*. These are best treated with a penicillin and metronidazole or clindamycin. The drug of choice for infection due to *Arcanobacterium haemolyticum* are macrolides (erythromycin or azithromycin); other drugs like clindamycin, doxycycline, ciprofloxacin and vancomycin are also effective.

Diphtheria is caused by toxin-producing strains of *Corynebacterium diphtheriae* and rarely by toxigenic strains of other *Corynebacterium* species (*C. ulcerans*, *C. haemolyticum* or *C. pseudotuberculosis*). It is rather rare now in the developed countries but is endemic in many parts of Africa, Asia (Afghanistan, Bangladesh, Bhutan, Cambodia, China, India, Indonesia, Laos, Mongolia, Myanmar, Nepal, Pakistan, Papua New Guinea, Philippines, Thailand and Vietnam), the Middle East (Iran, Iraq, Syria and Yemen) and Europe (Turkey, Albania and all countries of the former Soviet Union).

CHRONIC AND RECURRENT TONSILLITIS

This entity in children is not very well-defined, but may be described as a sore throat for 3 months or more, associated with inflammation of the tonsils. The etiology of recurrent tonsillitis is polymicrobial in origin (**Box 2**), with mixed anaerobic and aerobic infection or penicillin-resistant GABHS. Persistence of streptococcal carriage in the setting of a viral infection, nonadherence with the prescribed regimen, new infection acquired from close contacts and, rarely, treatment failure of the original infection may be the cause. Bacteria, lymphocytes, desquamated epithelial cells and other debris accumulate in the crypts of the tonsils resulting in cryptic tonsillitis. These cryptic plugs can then calcify into concretions or tonsilloliths. The presenting features are chronic sore throat, halitosis, a foreign body sensation in the throat, or a history of expelling smelly foul-tasting cheesy lumps. Examination reveals tonsils of varying sizes with the crypts having large quantities of debris. The drug of choice in these patients is clindamycin. New guidelines recommend watchful waiting for a 12-month period for recurrent tonsillitis in children not meeting the Paradise criteria (**Box 3**). However, patients with a history of recurrent

severe infections requiring hospitalization, or those who have had sequelae, such as peritonsillar abscess or Lemierre syndrome, may be considered for tonsillectomy before the end of the 12-month period even if they do not meet the frequency criteria.

COMPLICATIONS

The complications are divided into suppurative, local (peritonsillar, retropharyngeal and parapharyngeal cellulitis and/or abscesses, cervical lymphadenitis and mastoiditis) and nonsuppurative, systemic (acute rheumatic fever, scarlet fever, post-streptococcal glomerulonephritis and pediatric autoimmune neuropsychiatric disorder associated with group A streptococci (PANDAS)) complications. The nonsuppurative complications are beyond the scope of this chapter, and are discussed in their respective sections.

Peritonsillar Abscess (Quinsy)

This is a collection of pus between the superior constrictor muscle of the pharynx and the fibrous capsule of the tonsil. The origin is usually believed to be from the tonsillar crypts into the peritonsillar space through the tonsillar capsule, though another theory postulates its origin from supratonsillar fossa from an abscess in the salivary glands.

The symptoms are unilateral throat pain, odynophagia, trismus, otalgia, drooling and fever. There is a deviation of the uvula with an asymmetric peritonsillar swelling. The swelling of the anterior faucial pillar and palate displaces the tonsil downwards and medially. The confirmation of the diagnosis is by radioimaging or needle aspiration, the latter also being therapeutic. However, incision and drainage under general anesthesia with simultaneous tonsillectomy (quinsy tonsillectomy), makes most sense in small children. Anaerobes are commonly implicated, the drugs of choice being penicillin plus metronidazole or clindamycin.

Parapharyngeal Abscess

Infection of the tonsils can spread into the parapharyngeal space, resulting in high-grade fever with pain and stiffness of the neck along with swelling of the lateral pharyngeal wall. Diagnosis is by contrast-enhanced computed tomography (CECT) of the neck and treatment is by external incision and drainage and IV antibiotics.

BOX 2 Common causes of recurrent tonsillitis

Viral

- Adenovirus
- Rhinovirus
- Coronavirus
- Influenza virus
- Epstein-Barr virus

Bacterial

- Group-A beta-hemolytic streptococci
- *Moraxella catarrhalis*
- *Haemophilus influenzae*

BOX 3 Paradise criteria for tonsillectomy

Criterion definition

- Minimum frequency of sore throat episodes 7 or more episodes in the preceding year, (OR)
- 5 or more episodes in each of the preceding 2 years, (OR)
- 3 or more episodes in each of the preceding 3 years

Clinical features (sore throat plus the presence of 1 or more qualifies as a counting episode)

- Temperature more than 38°C, (OR)
- Cervical lymphadenopathy (tender lymph nodes or > 2 cm), (OR)
- Tonsillar exudates, (OR)
- Positive culture for group A beta-hemolytic *Streptococcus*

Treatment

- Antibiotics administered in conventional dosage for proved or suspected streptococcal episodes

Documentation

- Each episode and its qualifying features substantiated by contemporaneous notation in a clinical record, (OR)
- If not fully documented, subsequent observance by the clinician of 2 episodes of throat infection with patterns of frequency and clinical features consistent with the initial history
- Sleep apnea due to (adeno) tonsillar hypertrophy is now considered also a valid indication.

Lemierre' Syndrome

This is a septic thrombophlebitis of the jugular vein. Patients, usually adolescents, are very toxic with sudden onset high-grade fever with chills, neck pain and stiffness. There is associated respiratory distress as a result of multiple septic pulmonary emboli. This is usually a complication of a parapharyngeal space or odontogenic infection from *Fusobacterium necrophorum*. Treatment is by high-dose intravenous antibiotics (ampicillin-sulbactam, clindamycin or ciprofloxacin) and heparinization.

ADENOIDITIS

Acute Adenoiditis

The sudden onset of symptoms of acute adenoiditis is difficult to distinguish from those of a general upper respiratory tract infection and rhinosinusitis. Patients present with nasal obstruction, nasal discharge that may be clear or purulent, high-grade fever, cough, postnasal drip, mouth breathing, and often associated otitis media. Chronic adenoiditis is defined as symptoms lasting for more than 3 months, and results in the adenoid harboring bacteria and acting as a reservoir of infection for the paranasal sinuses. The adenoids play an important role in the development of otitis media. It was initially thought that the proximity of the adenoids in the nasopharynx with the middle ear and the eustachian tube predisposes the child to otitis media as a result of mechanical obstruction. It is now thought that the effect is likely one of local inflammation and mucosal edema as a result of regional spread of a bacterial biofilm leading to eustachian tube dysfunction and development of otitis media, rather than one of direct compression. If a child presents with the classic complaints of otitis media, with or without effusion, with acute or chronic nasal obstruction, mouth breathing, and a postnasal drip, an evaluation of the nasopharynx is warranted in addition to the middle ears.

Recurrent or Chronic Adenoiditis

This diagnosis is based on clinical features more than examination findings as the adenoid tissue is situated at a place where visualization and direct culture is difficult. Most children present with a blocked nose, mucopurulent posterior nasal drip, chronic cough, halitosis. They tend to continuously *snort* or *gag* on the mucus and develop a nasal intonation of speech. This results from the hyperplastic adenoids encroaching on the posterior nasal choanae resulting in collection of secretions in the nose. Common organisms implicated are *Haemophilus influenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus*, and streptococci including GABHS and *Streptococcus pneumoniae*.

Common antibiotics intended for treating upper respiratory pathogens are useful for patients with chronic adenoiditis (see *Chronic tonsillitis* above). Many organisms, particularly *Haemophilus influenzae*, form biofilms inside the adenoid tissue resulting in resistance to therapy. Inflammation of the adenoids can also result from allergic rhinitis and gastroesophageal reflux disease.

Airway Obstruction

Hypertrophied tonsils and adenoids are a major common cause of upper airway obstruction in children. This manifests as (SDB/OSA) syndrome, and upper airway resistance syndrome (See Chapter 39.11). The children present with a history of daytime symptoms (like nasal obstruction, hyposmia, chronic mouth breathing, rhinolalia clausa, poor appetite, poor school performance, and occasionally symptoms of right heart failure) and night-time symptoms (like snoring, choking, gasping, apnea, abnormal sleep postures, restless sleep, somnambulism, night terrors, excessive sweating and enuresis). As a result of chronic mouth breathing there is a change in facial development, leading to an increase in

the total anterior facial height and a tendency towards retrognathia of the mandible, resulting in the typical adenoid facies (**Figs 1A and B**). The size of the tonsils as seen on direct examination of the oropharynx, may not be indicative of the degree of airway obstruction. The oropharyngeal airway is designated by the linear distance between the two anterior tonsillar pillars (**Box 4**). Tonsillar hypertrophy is defined as 3+ or 4+. Tonsils need not be kissing to be graded 4+. Although this grading system is easy to follow and understand, many studies have shown that the volume of the adenoids and tonsils relative to the oropharynx is a better determinant of the severity of the sleep-disordered breathing and obstructive sleep apnea.

Evaluation of the size of the adenoids is done by a radiograph of the neck or fiber-optic nasopharyngoscopy. The simple plain lateral X-ray of the neck is still an excellent tool for screening and identification of the adenoids (**Fig. 2**) and based on the percentage of air column available in front of the adenoids, a 25%, 50% or 75% reduction is classified as mild, moderate or severe adenoid hypertrophy respectively. Another technique is by comparing the air column with the thickness of the soft palate. The air column is normal if it is more than the thickness of the soft palate. When the thickness is similar, it is mild enlargement. When it is narrower than the soft palate but wider than half the soft palate, it is moderate hypertrophy and if further narrowed and less than half thickness of soft palate, it is severe hypertrophy. However, X-rays can underestimate hypertrophy compared with nasopharyngoscopy. The palatine tonsils in the oropharynx cannot be assessed with X-ray.

Nasopharyngoscopic examination of the adenoids gives a better estimation of the degree of adenoid hypertrophy. It is graded from adenoids not in contact with adjacent structures (Grade 1) to the most severe where the adenoid tissue is in direct contact with the palate at rest (Grade 4).



Figures 1A and B A child with typical adenoid facies: (A) Anteroposterior; (B) Lateral views. Note: The allergic shiners, open mouth, increase in anterior facial height and a tendency towards retrognathia of the mandible

BOX 4 Mallampati scoring (or Brodsky grading scale) of tonsillar size

Tonsil 0:	Tonsils fit within the tonsillar fossa
Tonsil 1+:	Tonsils < 25% of space between the pillars/oropharyngeal width
Tonsil 2+:	Tonsils < 50% of space between the pillars/oropharyngeal width
Tonsil 3+:	Tonsils < 75% of space between the pillars/oropharyngeal width
Tonsil 4+:	Tonsils > 75% of space between the pillars/oropharyngeal width



Figure 2 X-ray of the neck showing severe adenoid hypertrophy

TONSILLOADENOIDECTOMY

Tonsillectomy, with or without adenoidectomy, is the second most common surgical procedure performed in children. Complete removal of the tonsil, including its capsule, by dissecting the peritonsillar space between the tonsil capsule and the muscular wall is called tonsillectomy. Tonsillotomy is subtotal removal of the tonsils without violating the tonsillar capsule.

The indications for tonsillectomy are enumerated in **Box 3**. Indications for adenoidectomy include along with tonsillectomy for SDB/OSA, chronic otitis media with effusion and eustachian tube dysfunction, and recurrent acute sinusitis with failure of medical treatment.

The various techniques used are cold dissection (traditional method using scalpel, guillotine and snare), electrocautery (using electric energy to generate temperatures of 400°C–600°C directly to the tonsillar area), Coblation (using bipolar radiofrequency energy to generate a high-energy ionized plasma field at a much lower temperature of 40°C–70°C), and microdebrider (using a rapidly rotating blade that suctions out excised tonsillar tissue while preserving the capsule). Because of the much lower temperatures used, there is reduced thermal damage to surrounding tissue and muscle, resulting in much less pain particularly in the immediate postoperative day with coblation.

Complications of tonsilloadenoidectomy are rare, and include postoperative hemorrhage (immediate postoperative period or delayed after separation of the eschar), anesthetic and airway risks, aspiration, airway obstruction (due to edema of tongue, palate or pharynx, or retropharyngeal hematoma), cardiac arrhythmia, vocal cord trauma, pulmonary edema, subluxation of the atlanto-axial joint (Grisel syndrome), dislocation of the mandible, injury to the eustachian tube, nasopharyngeal stenosis, palatopharyngeal insufficiency, central apnea, refractory torticollis and psychological trauma. Hypernasal speech immediately after surgery is common secondary to pain and restricted movement of the tonsillar pillars and soft palate, and subsides with conservative management. Velopharyngeal insufficiency is an uncommon complication where patients present with hypernasal speech and reflux of fluids through the nose. Children with history of cleft palate or submucosal cleft should not undergo adenoidectomy to prevent this complication. Estimated mortality rates range from 1 in 16,000 to 1 in 35,000 and are due to bleeding, aspiration, electrolyte imbalance or anesthetic

complications (like malignant hyperthermia, cardiac arrhythmia, vocal cord trauma, aspiration with resulting bronchopulmonary obstruction or infection, etc.). Postoperative respiratory complications following adenotonsillectomy are more common in obese children with OSA, hypotonia or craniofacial anomalies (e.g., Treacher Collins syndrome, Crouzon syndrome, Apert syndrome, etc.) in whom the procedure may not be curative for SDB. The potential benefits include reduction in frequency of ear, nose and throat illness, reduction in nasal obstruction with improvement in respiratory function, sleep, craniofacial growth and development, improvement in hearing impairment and improved growth and overall well-being.

Grisel syndrome or atlantoaxial subluxation is an uncommon complication of adenotonsillectomy resulting from decalcification of the anterior arch of the atlas and laxity of the anterior transverse ligament between the atlas and axis in the cervical spine. Patients present with a stiff neck, spasms of the sternomastoid or deep cervical muscle. Patients typically hold their head to one side with slight rotation toward the opposite side. Patients with Down syndrome are more susceptible to traumatic atlantoaxial subluxation after AT and thus great care is taken with cervical spine manipulation during surgery in patients with Down syndrome. Treatment consists of intravenous antibiotics and possible cervical traction as most cases are secondary to infection or trauma.

IN A NUTSHELL

1. Adenoids and tonsils are part of the Waldeyer ring that serve as a defense against inhaled and ingested pathogens and is an important source of precursors of B-cells.
2. The common disturbances are infections and hyperplasia. Self-limiting viral infections are the most common, followed by GABHS. Infectious mononucleosis caused by Epstein-Barr virus usually affects older children and adolescents.
3. Neoplasm is very rare in children, of which lymphomas are the primary cause.
4. Sleep-disordered breathing/obstructive sleep apnea is currently the most common indication for adenotonsillectomy in pediatrics.
5. Children with even moderately severe recurrent tonsillitis (except those meeting the Paradise criteria) may benefit from watchful waiting for a period of 1 year.
6. Adenotonsillectomy may not be curative in obese children with OSA, neuromuscular disorders, Down syndrome and craniofacial abnormalities; it may even be associated with an increased risk of postoperative respiratory complications.
7. Surgical techniques are safe and risk of complications are low in properly selected patients.

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Chapter 39.11

Obstructive Sleep Apnea

Zeynep Seda Uyan, Refika Ersu

Obstructive sleep apnea (OSA) is now widely recognized as a cause of significant morbidity among children, especially in the last few decades. It is characterized by episodes of complete or partial upper airway obstruction during sleep, often resulting in gas exchange abnormalities and disruption of sleep patterns. Childhood OSA is frequently diagnosed in association with adenotonsillar hypertrophy and obesity. It is also common in children with craniofacial abnormalities and neurologic disorders affecting upper airway patency. Untreated OSA can be associated with cardiovascular complications, impaired growth, learning problems, and behavioral problems. Therefore, early diagnosis and treatment of OSA may decrease morbidity. However, its diagnosis is frequently delayed.

EPIDEMIOLOGY

Obstructive sleep apnea exists in 1–4% of children and can occur in children of all ages, from neonates to adolescents, with a peak prevalence around 2–8 years. Habitual snoring during sleep which is the hallmark indicator of increased upper airway resistance can be seen in 7–8% of children. The ratio between habitual snoring and OSA is between 4:1 and 6:1 and accurate identification of habitually snoring children who have OSA is particularly challenging. The American Academy of Pediatrics (AAP) recommends that caregivers of children be asked about snoring during routine health-care visits and when the possibility of OSA is raised by suggestive symptoms.

ETIOLOGY

Adenotonsillar hypertrophy and obesity are the major risk factors for OSA in otherwise healthy children (**Box 1**). OSA also occurs in children with upper airway narrowing caused by craniofacial anomalies or in those with neuromuscular abnormalities such as hypotonia or muscular lack of coordination. Infection of the airways, allergy, supraglottic edema, mucopolysaccharide storage disease, laryngomalacia, subglottic stenosis, hypothyroidism may also result in altered soft tissue size leading to OSA. Genetic factors and ethnicity may also play a part. OSA is more common in African-Americans.

BOX 1 Risk factors associated with obstructive sleep apnea

- Adenotonsillar hypertrophy
- Obesity
- Allergic rhinitis
- Craniofacial anomalies (retrognathia, micrognathia, midface hypoplasia, etc.)
- Cerebral palsy
- Down syndrome
- Neuromuscular disorders
- Myelomeningocele
- Mucopolysaccharidoses
- Prader-Willi syndrome
- Achondroplasia
- Orthodontic problems (high narrow hard palate, overlapping incisors, cross bite, etc.)
- History of low birthweight
- Foreign body
- Family history of OSA

Abbreviation: OSA, obstructive sleep apnea.

PATHOPHYSIOLOGY

Childhood OSA results from a combination of structural and neuromuscular abnormalities. It occurs when the upper airway collapses during inspiration. The patency of the upper airway during sleep is controlled by complex interactions between upper airway resistance, pharyngeal collapsibility, tone of pharyngeal dilator muscles, and negative intraluminal pressure generated by the muscles of inspiration. In some children, this balance of mechanical forces can be disrupted. For instance, enlarged adenotonsillar tissue and obesity may increase resistance to airflow and pharyngeal collapsibility. The tendency of the airway walls to collapse under the influence of negative intraluminal pressure is counterbalanced by increased neuromuscular activation of the pharyngeal dilator muscles. Abrupt, intermittent reductions in activation of the pharyngeal dilator muscles during sleep in susceptible individuals leads to episodic airway collapse and hypopneic or apneic events.

CLINICAL FEATURES

Almost all children with OSA snore, although caregivers frequently do not give this information voluntarily at medical visits. Therefore, asking about snoring at each visit is a kind of screening method for OSA but it is important not to forget that OSA is less common than snoring. Thus, a positive answer should be followed by a detailed history and examination to determine whether further evaluation for OSA is needed. Both night-time and daytime symptoms should be evaluated together with physical examination findings (**Box 2**). It is important to note tonsil size during physical examination or to describe oropharyngeal crowding preferably according to objective classifications, e.g., Brodsky classification and Mallampati classification, respectively. Although there is generally no correlation between size of the adenotonsillar tissue and the presence or severity of upper airway obstruction during sleep, the amount of adenotonsillar tissue may be important in guiding management. Further information regarding obstruction can be obtained during direct laryngoscopy performed by an otolaryngologist.

BOX 2 Symptoms and signs of obstructive sleep apnea*Night-time symptoms*

- Habitual snoring (≥ 3 nights/week)
- Restless sleep and frequent awakenings
- Excessive sweating
- Night terrors
- Nocturnal enuresis
- Sleeping in a seated position or with the neck hyperextended
- Observed episodes of apnea

Daytime symptoms

- Mouth breathing and limited nasal airflow
- Chronic rhinorrhea
- Headache on awakening
- Daytime sleepiness
- Recurrent ear infections
- Attention deficit hyperactivity disorder
- Learning problems

Physical examination findings

- Underweight or overweight
- Adenoidal facies
- Tonsillar hypertrophy
- Retrognathia/micrognathia
- Pectus excavatum
- Enlarged neck circumference
- Hypertension

APPROACH TO DIAGNOSIS

A complete diagnostic evaluation for OSA consists of a focused sleep history, physical examination, and polysomnography (PSG). Additional testing is sometimes indicated. The diagnostic process may be modified depending on the clinical level of suspicion for OSA and local resources. Children who snore on most or all nights (equal to or more than 4 days a week) should undergo diagnostic evaluation, which includes a careful history and physical examination. Although history and physical examination are useful to screen patients and determine which patients need further investigation for OSA, the sensitivity and specificity of the history and physical examination are poor. Physical examination when the child is awake may be normal. The size of the tonsils cannot be used to predict the presence of OSA in an individual child. Thus, objective testing is required. The gold standard test is overnight PSG which is, at least presently, the only definitive diagnostic approach for OSA.

Polysomnography

Polysomnography should be performed and interpreted by clinicians with training in sleep medicine. It is a noninvasive test involving the measurement of a number of physiologic functions overnight including electroencephalography, pulse oximetry, oronasal airflow, abdominal and chest wall movements, partial pressure of carbon dioxide and video recording. Specific pediatric measuring and scoring criteria should be used while evaluating the results of children. PSG will demonstrate not only the presence or absence of OSA but also the severity of OSA, which is helpful in planning treatment and in postoperative short- and long-term management.

Indices Used to Characterize Obstructive Sleep Apnea

Apnea is a above 90% decrease in airflow that lasts equal to or above 90% of the duration of two normal breaths, as determined from the baseline breathing pattern. Apnea is considered *obstructive* if there is continued or increased inspiratory effort during the entire period of decreased airflow (**Fig. 1**). It is considered *central* if inspiratory effort is absent during the entire period of airflow cessation (**Fig. 2**). It is considered *mixed* if the inspiratory effort is absent during one portion of the event and the inspiratory effort is present in another

portion (**Fig. 3**). Hypopnea is a more than or equal to 30% decrease in airflow that lasts more than or equal to 90% of the duration of two normal breaths AND the decreased airflow is associated with an arousal or at least 3% oxyhemoglobin desaturation (**Fig. 4**).

The *apnea-hypopnea index* (AHI) is the number of apneas plus hypopneas that occur per hour of sleep. *Respiratory effort-related arousal* (RERA) is a respiratory event associated with an arousal lasting the duration of two breaths, with increasing respiratory effort, flattening of the inspiratory portion of the nasal pressure waveform, snoring, or an elevation in the end-tidal PCO₂ leading to an arousal from sleep, when the sequence of breaths does not meet criteria for an apnea or hypopnea. The *respiratory disturbance index* (RDI) is the number of apneas, hypopneas, and RERAs per hour of sleep. *Obstructive hypoventilation* exists when the end-tidal or transcutaneous CO₂ exceeds 50 mm Hg for more than 25% of the total sleep time. *Hypoxemia* is defined as an oxyhemoglobin saturation (SpO₂) of less than 92%. Additional events reported during PSG include arousals, snoring, changes in body position, and limb movements. Indices other than AHI that can be calculated from the PSG data include sleep efficiency, sleep stage percentage, sleep stage latency, sleep stage distribution, the apnea index and the arousal index.

If overnight PSG is not available, sleep questionnaires, in-home overnight audiotaping, videotaping, pulse oximetry, daytime nap PSG or ambulatory PSG can be used for the diagnosis of OSA keeping in mind that these alternative tests have a low negative predictive value.

MANAGEMENT

Indications for Treatment

Treatment is considered if the child is at increased risk for having OSA and fits at least one of the following criteria:

1. AHI more than 5 episodes/hour in any child, irrespective of the presence of OSA-related morbidity.
2. AHI 1–5 episodes/hour and systolic or diastolic blood pressure consistently above 95th percentile for gender, age, and height, or documented pulmonary hypertension.
3. AHI 1–5 episodes/hour and morbidity from the central nervous system (excessive daytime sleepiness, hyperactivity, inattention, and academic difficulties).

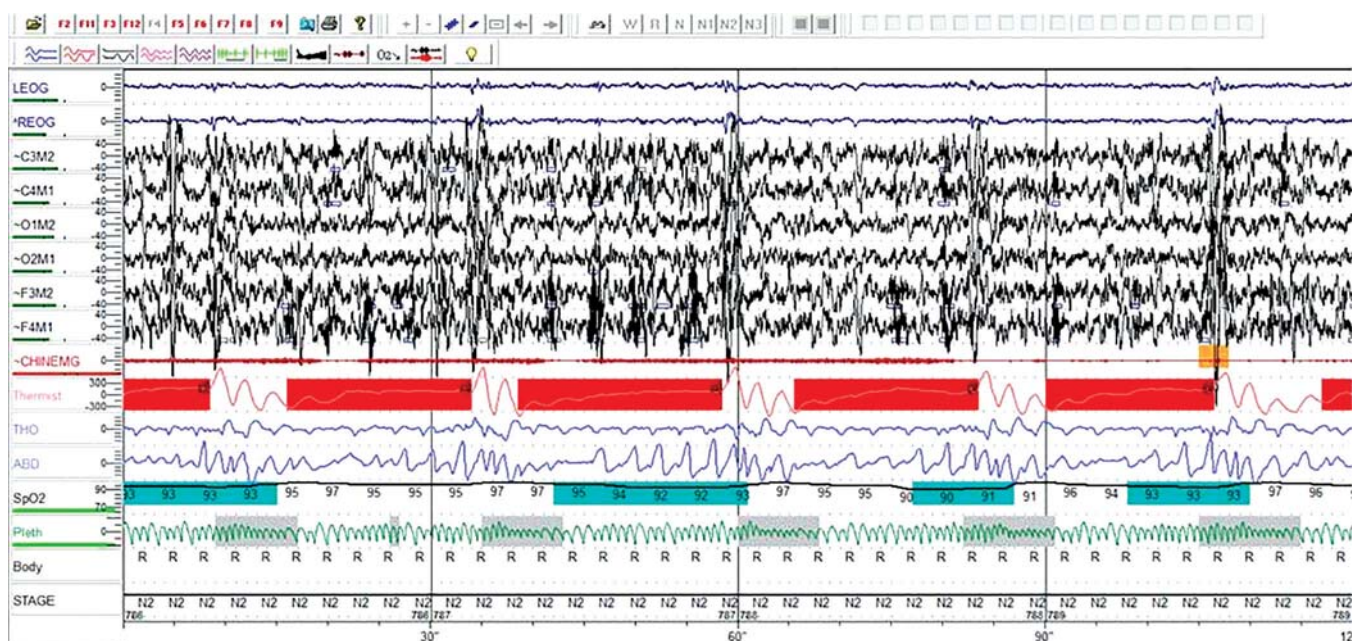


Figure 1 Episodes of obstructive sleep apnea (marked with red) accompanied by desaturations during 120 seconds of sleep

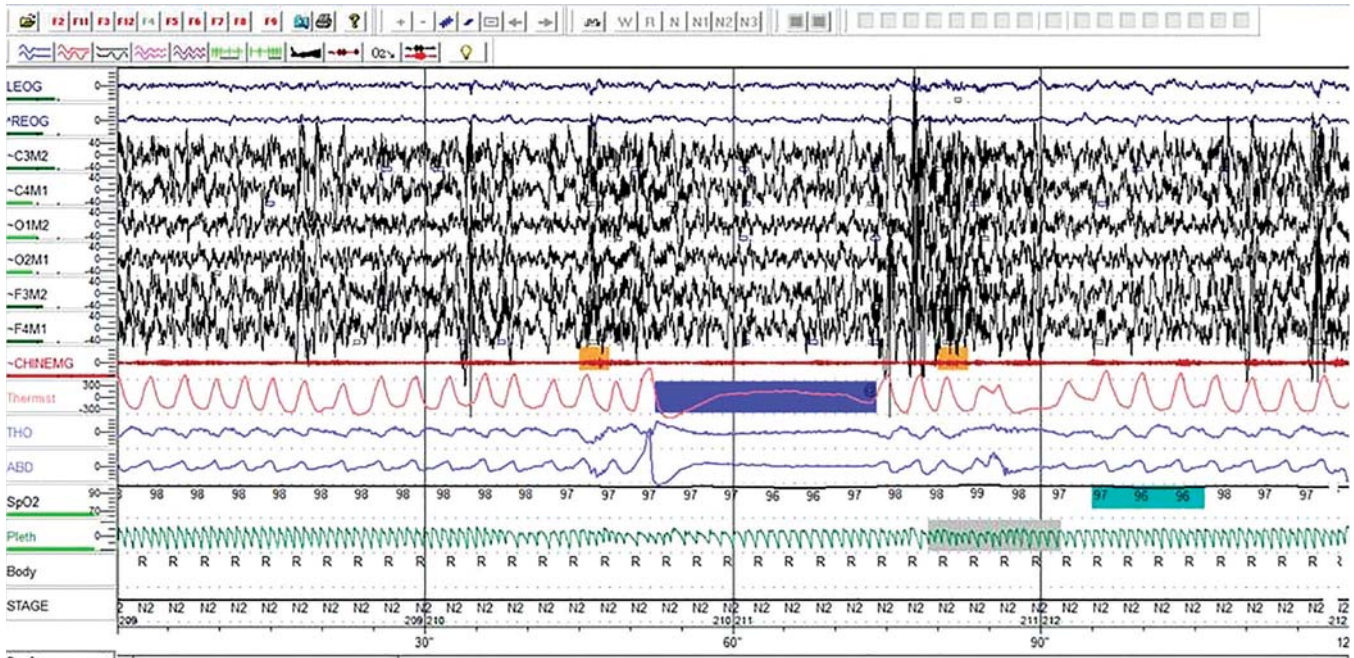


Figure 2 An episode of central apnea (marked with blue) during 120 seconds of sleep

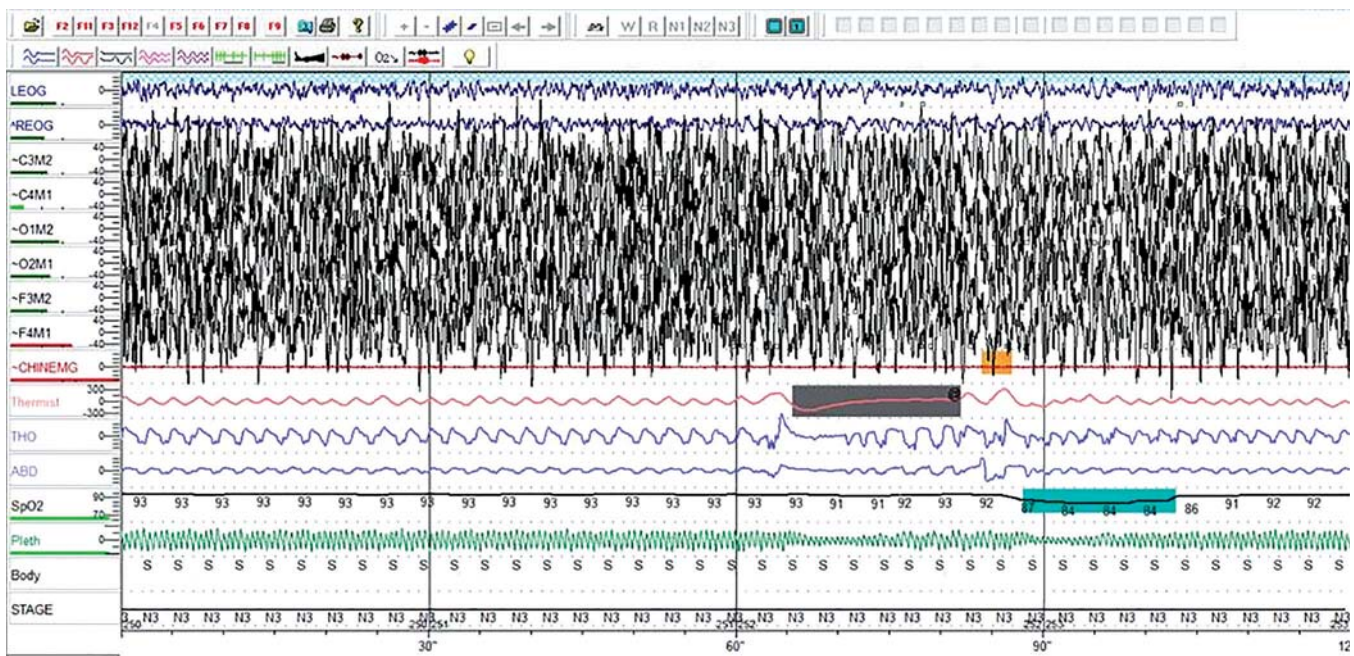


Figure 3 An episode of mixed apnea during 120 seconds of sleep

4. AHI 1–5 episodes/hour and inadequate somatic growth.
5. AHI 1–5 episodes/hour and nocturnal enuresis.
6. AHI 1–5 episodes/hour and presence of risk factor(s) for persistence of OSA in adolescence.
7. AHI 1–5 episodes/hour and diagnosis of muscular or neuromuscular disorder or major craniofacial abnormality or combination of pathogenetic mechanisms.
8. Nocturnal pulse oximetry with three or more SpO₂ drops below 90% and three or more clusters of desaturation events.

Chest radiography, electrocardiography and echocardiography can also be performed while evaluating the children with suspected OSA and evidence of underlying cardiopulmonary disease since children with lower airway disease may have

episodes of hypoxemia during sleep, independent of upper airway obstruction. These tests should also be considered for children with confirmed severe OSA.

Adenotonsillectomy

If a child is diagnosed to have OSA, has a physical examination consistent with adenotonsillar hypertrophy and does not have a contraindication to surgery, adenotonsillectomy is the first line of treatment. Both tonsils and adenoids should be removed, even when one or the other seems to be the primary problem because OSA is the conglomerate result of the relative size and structure of the upper airway components, rather than the absolute size of the adenotonsillar tissue. Adenotonsillectomy improves OSA in

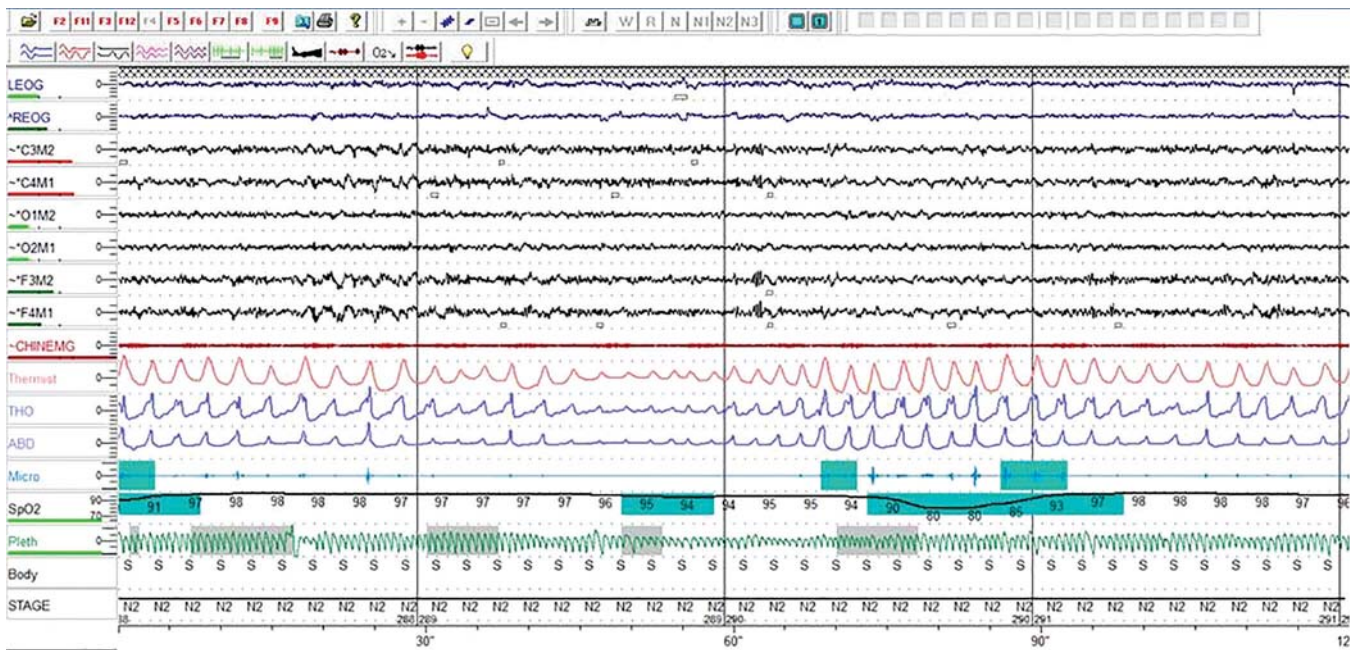


Figure 4 An episode of hypopnea during 120 seconds of sleep

most children by increasing the patency of the upper airway. Risk factors for ongoing OSA after adenotonsillectomy include severe OSA on preoperative PSG or the presence of complicating factors such as abnormal upper airway tone, craniofacial anomalies, and obesity. Postoperative polysomnographic evaluation 10–12 weeks after surgery is probably needed in these patients. Children with OSA are at risk for respiratory compromise postoperatively as a result of upper airway edema, increased secretions, respiratory depression secondary to analgesic and anesthetic agents and postobstructive pulmonary edema. Children younger than 3 years of age, those with more severe OSA on PSG (AHI equal to or more than 24 events per hour, oxygen saturation nadir of less than 80%, or peak PCO_2 of equal to or more than 60 mm Hg), with cardiac complications due to OSA and those with additional medical conditions such as craniofacial syndromes or neuromuscular disease are at high-risk for such complications. Therefore, careful cardiorespiratory monitoring should be performed for at least 24 hours postoperatively in these patients.

Other Treatment Modalities

If a child has OSA but does not have adenotonsillar hypertrophy or if symptoms and signs of OSA persist after adenotonsillectomy, other treatment options should be considered.

Noninvasive positive pressure ventilation which is a long-term therapy, is the most common nonsurgical therapy for OSA in children. It involves administering airway pressure through a nasal mask, which prevents upper airway obstruction and reduces both sleep disruption and the work of breathing. Continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BPAP) are the usual types of positive airway pressure. The pressure required to treat OSA is initially determined by titration during PSG in the sleep laboratory. The pressure level should be periodically controlled with repeat PSG.

Supplemental oxygen can result in improved arterial oxygen saturation in children with OSA without worsening the degree of obstruction. However, it should be reserved as a temporary palliative measure before adenotonsillectomy and should not be used as a first line treatment because it does not address many of the pathophysiologic features associated with OSA. It should not be used without monitoring the potential changes in PCO_2 because

some patients with OSA can develop unpredictable and potentially life-threatening hypercapnia while breathing supplemental oxygen.

Craniofacial reconstructive procedures are reserved for some children with craniofacial anomalies. Tracheotomy is an option for children with severe OSA who have failed to respond to other treatment approaches. It bypasses areas where upper airway obstruction occurs during sleep. It is most often necessary in children with complex anatomic or neuromuscular problems.

Weight loss is recommended as an adjunctive therapy for obese children with OSA since obesity contributes to the increased upper airway resistance which characterizes OSA.

Intranasal corticosteroids or *leukotriene modifier therapy* may be useful to treat mild OSA, and can be considered when adenotonsillectomy was not curative or adenotonsillectomy or noninvasive positive pressure ventilation are not treatment options for the child.

OUTCOME AND COMPLICATIONS

Obstructive sleep apnea can have adverse effects on somatic growth, and can lead to cardiovascular and metabolic alterations including pulmonary hypertension, systemic hypertension, insulin resistance, and hyperlipidemia. Increased energy expenditure during sleep and disruption of the growth hormone and insulin-like growth factor and binding proteins may lead to reduction in growth velocity. Elevation of pulmonary arterial pressure caused by hypoxia-induced pulmonary vasoconstriction is a serious consequence of OSA in children and may lead to cor pulmonale. Intermittent hypoxia may affect left ventricular function through both direct and indirect effects on myocardial contractility. It may also have long-term effects on neuronal and intellectual functions of children leading to school problems, restlessness, aggressive behavior and poor test performances. An association between OSA and attention deficit-hyperactivity disorder has been proposed. Although the mechanism by which OSA may contribute to hyperactivity is not clear, it is possible that both sleep fragmentation and episodic hypoxia that characterize OSA lead to alterations within the neurochemical substrate of the prefrontal cortex with resultant executive dysfunction.

IN A NUTSHELL

1. Adenotonsillar hypertrophy and obesity are the major risk factors for OSA in otherwise healthy children.
2. Asking about snoring at each visit is a kind of screening method for OSA without forgetting that OSA is less common than snoring.
3. Overnight PSG is the gold standard test for the diagnosis of OSA.
4. If a child is diagnosed to have OSA, has a physical examination consistent with adenotonsillar hypertrophy and does not have a contraindication to surgery, adenotonsillectomy is the first line of treatment.
5. Noninvasive positive pressure ventilation is the most common nonsurgical therapy for OSA in children.
6. Intranasal corticosteroids or leukotriene modifier therapy may be useful to treat mild OSA, and can be considered when adenotonsillectomy is not curative or adenotonsillectomy or CPAP/BPAP are not treatment options for the child.
7. Untreated OSA can be associated with cardiovascular complications, impaired growth, learning problems, and behavioral problems.

MORE ON THIS TOPIC

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Chapter 39.12

Congenital Malformations of the Lower Respiratory Tract

D Vijayasekaran

When a common respiratory problem in a child is not responding to usual line of management, the possible association of underlying congenital respiratory lesion should be considered. Majority of congenital malformations of the lower respiratory tract may present as a respiratory infection or a pneumonia mimicker during any time in childhood, usually in the early months of life. The congenital malformations of the lower respiratory tract include those related to airway and that of lung. The common congenital lung lesions include congenital pulmonary airway malformation (CPAM), pulmonary sequestration, bronchogenic cysts, congenital lobar emphysema (CLE), hypoplasia of the lung and the common airway lesions include tracheoesophageal fistula, tracheomalacia, laryngeal web and tracheal stenosis.

DEVELOPMENT OF RESPIRATORY SYSTEM

A brief revision of the embryogenesis of respiratory system may increase our understanding about this subject. Respiratory primordium is derived from primitive foregut and its morphogenesis can be divided into five stages:

1. **Embryonic stage (3–6 weeks):** A ventral outpouching from the endodermal epithelium of primitive foregut (bronchial bud) interacts with the tissue of mesodermal origin.
2. **Pseudoglandular stage (6–16 weeks):** The conducting airways continue to branch and the bronchial bud resembles a gland. Trachea and primitive foregut are separated by progressive fusion of epithelial ridges and similar process occurs between central tendon and pleuroperitoneal folds.
3. **Canalicular stage (16–26 weeks):** Tubules of bronchial bud expand to form sacculles. The airspaces increasingly come into close opposition to capillary network.
4. **Saccular stage (26–36 weeks):** The acinar tubules continue to proliferate and the surface area of the gas exchange region increases.
5. **Alveolar period (36 weeks to maturity):** The alveolar septation continue to occur even after the birth and continue up to 6 years.

The timing and severity of various insults to the developing lung may determine the lesions. Stages of lung development and the common lesions associated with maldevelopment are depicted in **Table 1**.

DIAGNOSTIC EVALUATION

The diagnostic evaluation of a child with suspected congenital malformations of the lower respiratory tract should begin with detailed clinical history including antenatal history. Recurrent respiratory tract infection is the common mode of presentation. In small group of patients, these malformations remain unrecognized for a long time. Pulmonary hypoplasia is associated with oligohydramnios.

The physical examination should focus on symmetry of chest, retractions and change in the resonance and air entry. Scaphoid abdomen may suggest diaphragmatic hernia. Frothing at the mouth of the neonate should alert the possibility of esophageal atresia. Since congenital malformations of respiratory tract are associated with other system disorders, a detailed examination should be done to identify any other associated defect.

Table 1 Stages of lung development and congenital lung lesion

Stage of lung development	Congenital lung lesion
Embryonic (3–6 weeks)	<ul style="list-style-type: none"> • <i>Atresia:</i> Tracheal, laryngeal, esophageal • Pulmonary agenesis/tracheal stenosis • Tracheoesophageal fistula • Bronchogenic cyst • Pulmonary sequestration (extralobar)
Pseudoglandular (6–16 weeks)	<ul style="list-style-type: none"> • Congenital pulmonary airway malformation • Tracheobronchomalacia • Diaphragmatic hernia • Pulmonary sequestration (intralobar)
Canalicular (16–26 weeks)	Pulmonary hypoplasia
Saccular (26–36 weeks)	Respiratory distress syndrome
Alveolar (up to 6 years)	<ul style="list-style-type: none"> • Congenital lobar emphysema • Bronchopulmonary dysplasia

Plain chest radiographs may give a clue about congenital lesion of the lung. Chest radiographic findings such as opacification, mass lesion, cystic lesions, shift of the mediastinum, unusual air collection should be carefully seen. Pulmonary sequestration and CPAM commonly occur in lower lobes and CLE in left upper lobe.

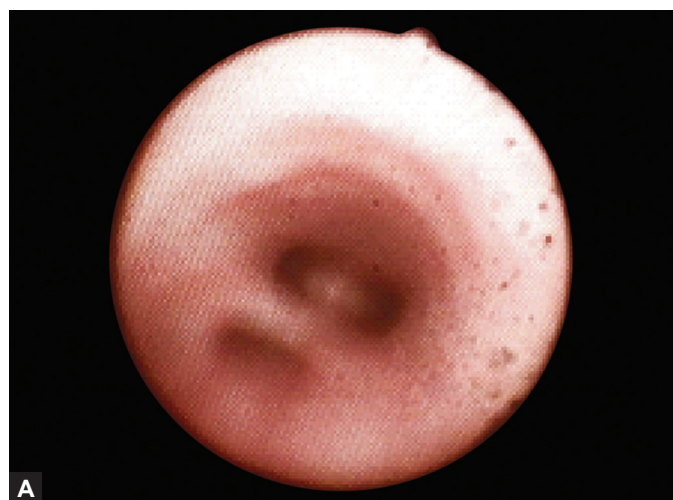
Other diagnostic imaging studies such as barium esophagography, computed tomography (CT) and magnetic resonance imaging (MRI) confirm the diagnosis. Three-dimensional reformatting of the CT scan and virtual bronchoscopy are used to reconstruct the images. Fiberoptic bronchoscopy plays a significant role in the evaluation of luminal pathology (**Figs 1A and B**) and in dynamic lesions such as airway malacias. The antenatal ultrasound scan plays an important role in the prenatal diagnosis.

CONGENITAL PULMONARY AIRWAY MALFORMATION

Congenital pulmonary airway malformation, previously known as congenital cystic adenomatoid malformation (CCAM), is a rare pulmonary disorder. The pathogenesis of CPAM is uncertain; it may result due to abnormality of the branching morphogenesis of the lung. The abnormal hamartomatous CPAM proliferation usually retains its communication with the normal bronchiolar tree but does not participate in normal gas exchange. CPAM is almost always unilateral (85–95%) but occasionally bilateral (2%). Three types of cystic adenomatoid malformation were identified initially (type 1–3), later two additional types were added (type 0 and 4). The current classification of CPAM of the lung is depicted in **Table 2**.

The most common presentation of CPAM in postnatal period is progressive respiratory distress with grunting, retractions and cyanosis. At times, differentiating CPAM from complicated staphylococcal pneumonia is difficult when a newborn presents with respiratory distress. Over a period, pneumatoceles due to a necrotic pneumonia (e.g., staphylococcal) may resolve but CPAM will persist on chest radiograph. The chest radiograph of CPAM of lung often shows shift of the mediastinum to the contralateral side (**Fig. 2**).

Surgical resection of CPAM lesions is necessary even for asymptomatic patients to prevent infection and avoid potential malignant transformation of the lesion. A limited resection of affected CPAM segment is done with due attention to preserve maximal normal lung tissue.



Figures 1A and B Bronchoscopic views of tracheoesophageal fistula (see Section 18 for details)

Table 2 Classification of congenital pulmonary airway malformation (CPAM) of the lung

CPAM type	Features and prognosis
Type 0	Involvement of all lung lobes, incompatible with life
Type 1	<i>Macrocytic:</i> Single/multiple cysts, 2 cm and above; lined by pseudostratified columnar; constitutes approximately 50% of postnatal cases with favorable prognosis
Type 2	<i>Microcystic:</i> Single or multiple cysts, 2 cm and less; cuboidal or columnar epithelial lining associated with higher congenital anomalies (approximately 40%)
Type 3	Predominantly solid lesions with small (< 0.5 cm) cysts, lined by cuboidal epithelium (10%), associated with pulmonary hypoplasia with poor prognosis, grossly elevated amniotic fluid α -fetoprotein
Type 4	Large air-filled cysts, lined by flattened epithelial cells



Figure 2 Chest radiograph of congenital pulmonary airway malformation of left lung showing shift of the mediastinum to right with cystic lesions in left lung

PULMONARY HYPOPLASIA AND AGENESIS

Pulmonary Hypoplasia

It denotes incomplete development of the lungs resulting in an abnormally low number of alveoli. It may be secondary to other fetal abnormalities that interfere with normal development of the lungs which include diaphragmatic hernia, CPAM, fetal hydronephrosis and developmental mediastinal masses. Chest radiograph shows ipsilateral shift of the mediastinum due to volume loss of lung. The orifice of involved main bronchus is narrow and small due to underdevelopment which may be demonstrated by fiberoptic bronchoscopy (**Figs 3A to C**). On CT of the chest, the pulmonary artery is hypoplastic on the affected side.

Agenesis of Lung

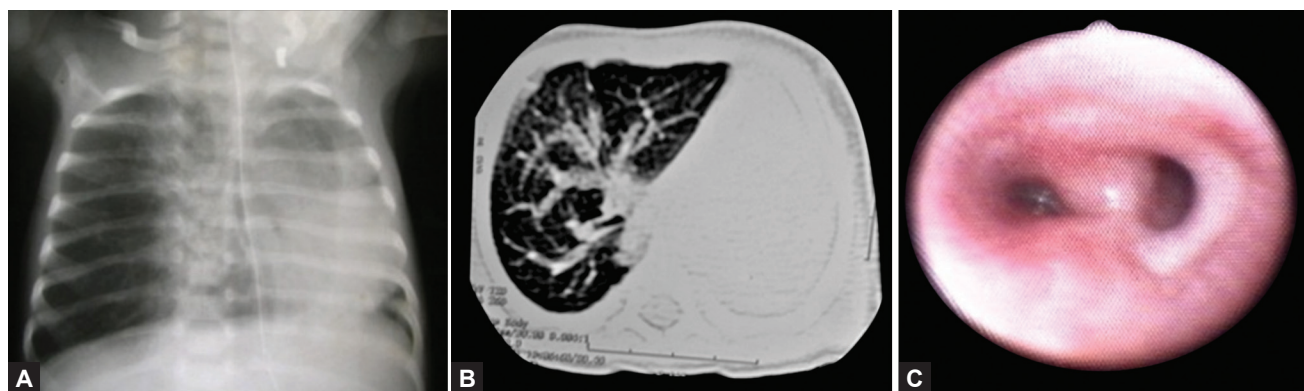
It is a primary defect in organogenesis where the affected side demonstrates complete absence of the bronchial system and lung. The trachea continues to normal bronchial system without carina. *Pulmonary aplasia* is category in between hypoplasia and agenesis where bronchial stump and carina are visualized without bronchial system on the affected side. Pulmonary hypertension complicates lung agenesis. Right lung agenesis has a higher morbidity and mortality.

PULMONARY SEQUESTRATION

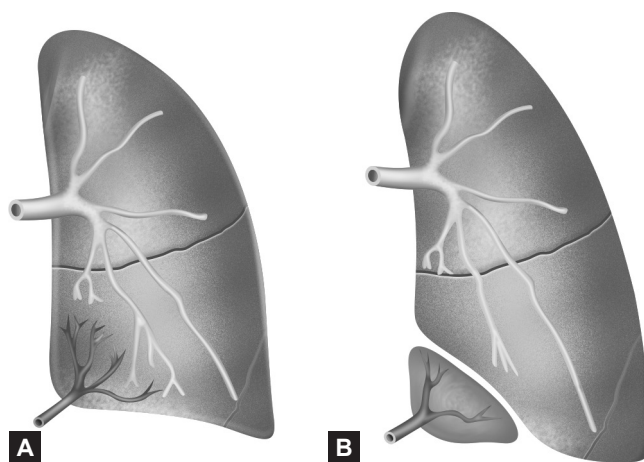
Pulmonary sequestration is a rare congenital malformation of the lower respiratory tract. It consists of a nonfunctioning mass of lung tissue that lacks normal communication with the tracheobronchial tree but demonstrates blood supply originating from the systemic artery system. When the lesion is located within a normal lung, it is designated intralobar sequestration (ILS) and when outside the lung, it is called the extralobar sequestration (ELS) (**Figs 4A and B**).

The majority of sequestrations occur in the lower lobes. The vascular supply for both generally arises from the lower thoracic or upper abdominal aorta. The knowledge about the major differences between ILS and ELS is helpful for both diagnosis and management (**Table 3**).

Computed tomography scan chest with CT angiography is fairly accurate for the diagnosis of pulmonary sequestration. Contrast-enhanced magnetic resonance angiography (MRA) may help in the diagnosis of pulmonary sequestration by demonstrating a systemic blood supply, particularly from the aorta.



Figures 3A to C Pulmonary hypoplasia. (A) Chest radiograph; (B) CT chest; (C) Bronchoscopy



Figures 4A and B (A) Intralobar pulmonary sequestration; (B) Extralobar pulmonary sequestration

Table 3 Differences between intralobar sequestration and extralobar sequestration

Features	Intralobar sequestration	Extralobar sequestration
Age at diagnosis	Child to adult	Neonate
Sex distribution	Equal	80% male
Frequency	More frequent	Less frequent
Visceral pleura	Lacks pleura	Has its own pleura
Location	Left lung (posterior basal segment)	Left side at costophrenic groove/below the diaphragm
Associated anomalies	Uncommon	Common
Venous drainage	Pulmonary	Systemic
Bronchial communications	Present	None
Surgery	Lobectomy	Sequestrectomy

CONGENITAL LOBAR EMPHYSEMA

The lesion occurs due to intrinsic or extrinsic narrowing of the affected bronchi. Intrinsic narrowing is due to the weakness or absence of bronchial cartilage. The upper left lobe is the most frequently affected (42%) followed by right middle (35%) and right upper lobe (21%). The overdistended portion of the affected lobe compresses the adjacent lobes and thus compromises the ventilation. Males are affected three times as often as females. The most frequently documented cause of CLE is ball-valve type obstruction which results in air-trapping of the developing airway. 50% of the patients become symptomatic in the neonatal period with progressive respiratory distress.

X-ray chest shows a hyperlucent overexpanded area, mediastinal shift and compression of the adjacent lobes (**Figs 5A and B**). CT chest plays a major role in the confirmation of typical CLE. The symptomatic neonate needs to be operated immediately. Asymptomatic CLE or one who has mild symptoms should be evaluated before surgery.

Severe bronchomalacia of the left main bronchus or the left upper lobe proper masquerades as CLE of left upper lobe. In our observation, few children with atypical features of CLE demonstrated either bronchomalacia of the left main bronchus or the left upper lobe or both. In such situations due to dynamic nature of the lesion, the bronchoscope could be negotiated distally (which is not possible with typical CLE) and the distal airway anatomy is found to be normal. Thus, fiberoptic bronchoscopy

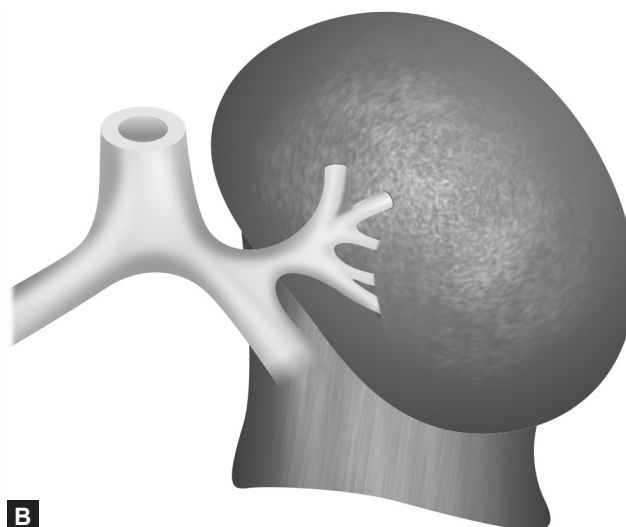
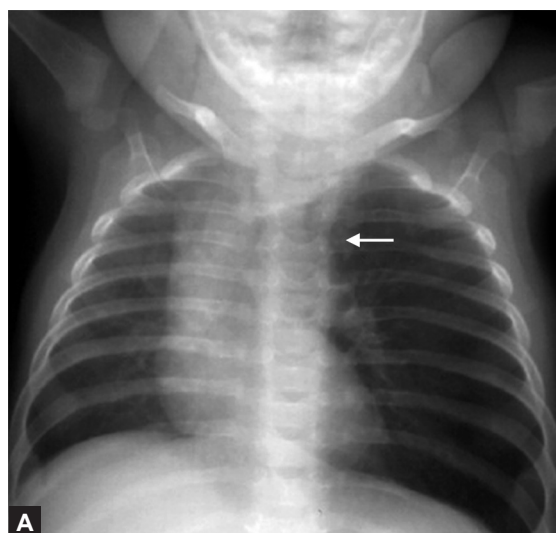
plays an important role in identifying children with clinical features of CLE who perhaps can be saved from an unnecessary lobectomy and instead offered more specific intervention such as airway stenting.

BRONCHOGENIC CYST

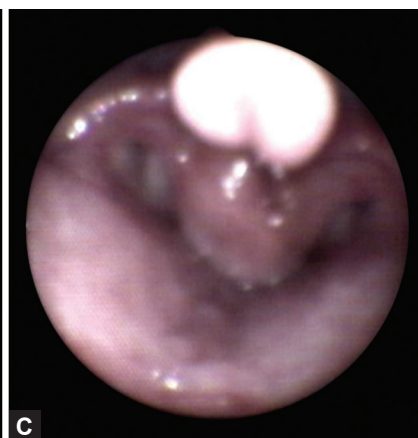
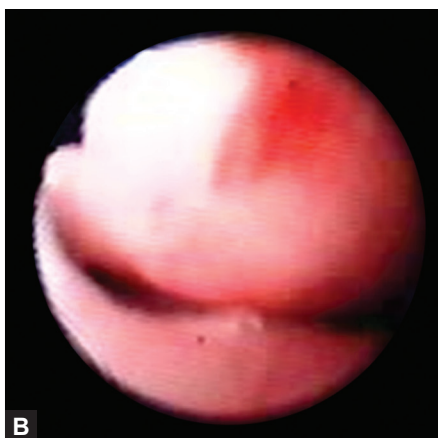
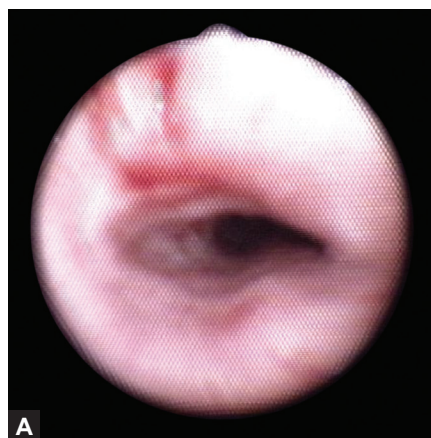
Bronchogenic cyst results due to abnormal growth of the aerial conducts, occurs at embryonic stage. Bronchogenic cyst usually has no communication with the bronchial tree. At times, bronchial communication develops tension cyst and infection. Bronchogenic cysts are closely attached to major airways and the esophagus by dense fibrous tissue and usually (65%) located in the mediastinum. Intrapulmonary cysts are usually rare, located in the lower lobes. Cyst infection is more frequently seen in intrapulmonary cysts. Chest X-ray may give a diagnostic clue, but confirmation can be made more accurately using CT chest. Not all bronchogenic cysts need intervention. The decision for surgery is predicated by the presence of compression symptoms due to large size cysts or in cases of infection.

AIRWAY MALACIAS

Airway malacias are increasingly recognized due to the availability of smaller size fiberoptic bronchoscopes (**Figs 6A to C**). The



Figures 5A and B Congenital lobar emphysema left upper lobe as seen in (A) X-ray chest and (B) diagrammatic illustration



Figures 6A to C Bronchoscopic views of (A) tracheomalacia, (B) bronchomalacia (bilateral) and (C) laryngomalacia

incidence reported in western literature is between 1:1,500 and 1:2,500, but the actual incidence is believed to be still higher. A recent study done in infants with moderate and severe laryngomalacia reported a high incidence of associated lower airway malacias (48%) of which tracheomalacia was the most common associated lower airway anomaly (29%).

Tracheomalacia is characterized by flaccidity of the tracheal support cartilage. If the condition extends further to the main bronchi, it is termed *tracheobronchomalacia* while those localized to one main bronchus without involving trachea are termed as *bronchomalacia*. Airway malacias may occur in various combinations. These disorders should be considered when unexplained symptoms of wheezing or coughing are present in young infants.

Tracheomalacia

Primary tracheomalacia is thought to be caused by congenital immaturity of the tracheal cartilage. In *secondary tracheomalacia*, previously normal cartilage undergoes degeneration. The intrathoracic trachea normally dilates slightly during inspiration and narrows slightly during expiration. These processes are exaggerated in tracheomalacia leading to airway collapse on expiration. Dynamic compression of the anterior wall of the trachea is a typical finding observed by fiberoptic bronchoscopy (gold standard) done under local anesthesia.

The diagnosis of airway malacias presents a clinical challenge because of the frequent overlap of symptoms with more common childhood respiratory illnesses such as wheezy disorders. The distinction may be of clinical relevance because bronchodilators like β -agonists can worsen the wheeze caused by airway malacias by reducing the muscle tone, thus making the bronchi more compliant. Ipratropium bromide appears to be beneficial in such conditions.

In airway malacias, impaired drainage of secretions resulting in backlog of secretions is an added problem. Understanding the basic pathology is important. A triad including avoidance of β -agonists, airway clearance and semisynthetic anticholinergics may form effective management surgery in airway malacias. In cases with severe malacia, these children may need airway stenting or airway distension by bilevel pressure support.

Tracheal Stenosis

Tracheal stenosis comprises a wide range of tracheal abnormalities, but the common denominator is congenital narrowing of the trachea. Based on the features such as the narrowness of the trachea, the extent of tracheal involvement, the involvement of the bronchi and the presence or absence of complete tracheal rings, many distinct types are described. Congenital subglottic stenosis, a variant of tracheal stenosis,

usually presents immediately after birth. Other forms of tracheal stenosis include funnel-shaped trachea, stenosis with complete cartilage rings and tracheal webs.

In our experience, most common presentation is the one with more circular tracheal cartilage rings with less pars trachealis muscle (membranous part of the trachea). Infants with tracheal stenosis present with biphasic stridor. The affected ones frequently get hospitalized for want of diagnosis. Multidisciplinary approach along with proper communication with the intensive care team may avoid repeated hospitalizations.

Though various surgical techniques are reported, conservative management is preferred especially in minor variants of tracheal stenosis as the tracheal lumen may widen along with the age.

IN A NUTSHELL

1. Tracheoesophageal fistulas, lobar emphysema, diaphragmatic hernia, agenesis of lung and laryngotracheal stenosis may present as neonatal emergency.
2. Lesions such as pulmonary airway malformation, pulmonary sequestration, bronchogenic cysts present as recurrent respiratory tract infection.
3. Airway malacias can present as nonresponsive infantile wheeze.
4. Commonly, a useful diagnostic clue is provided by the chest radiograph. Subsequent confirmatory investigations include barium esophagography, CT, MRI and fiberoptic bronchoscopy.
5. Surgery is indicated in majority of congenital lung masses due to the inherent risk of malignant transformation.

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Chapter 39.13

Stridor and Croup

Shalu Gupta

STRIDOR

The origin of word *stridor* is from a Latin word *stridulus*, which means creaking. Stridor is a high-pitched sound produced by abnormal air passage during breathing. Essentially, it is a loud inspiratory sound originating from the extrathoracic airways. A lesion in glottic or subglottic region usually produces a biphasic stridor.

Pathogenesis

Infants and children are particularly prone to develop early airway obstruction. The anatomy of larynx is different in children as compared with adults, which makes them susceptible to airway narrowing. The larynx in infants is situated high in neck, and the epiglottis is narrow, omega-shaped, and vertically placed. In children, the narrowest part of the airway is the subglottic area unlike adults where it is glottis. Further, it is supported by loose, nonfibrous mucosa which gets easily obstructed in subglottic edema. The cartilaginous support of infant airways is soft and compliant. In addition to these factors, children have a large head, relatively lax neck support, large tongue and poor cell-mediated immunity which further predispose them to airway obstruction. The resistance to airflow is inversely proportional to the radius of the airway to the fourth power ($R \propto 1/r^4$). So a small decrease in airway caliber will cause profound increase in airway resistance.

Etiology

The usual lesions causing stridor can be situated in the extrathoracic airways, i.e., nasopharynx, larynx and trachea; or in the intrathoracic part. Stridor is a clinical sign and not a diagnosis. The causes of stridor can range from relatively benign to some very serious and even life-threatening causes (**Table 1**).

Approach to Stridor

The important issues when a child or infant presents with stridor are: (a) to evaluate the severity of airway obstruction, and if required immediate intervention to prevent it from further

worsening and progressing to respiratory fatigue and finally to failure and (b) timely referral when a significant airway lesion is suspected. A detailed history and examination can give a clue to a possible etiology (**Flow chart 1**).

Causes of stridor presenting at birth are usually congenital lesions such as choanal atresia, laryngeal web, laryngomalacia, tracheal stenosis, anomalous vascular rings or congenital vocal cord paralysis. In laryngomalacia and subglottic hemangioma, stridor becomes worse on straining or crying. Stridor also worsens in supine posture in laryngomalacia, tracheomalacia, micrognathia and macroglossia. Feeding increases the stridor in tracheoesophageal fistula, neurologic disorders, gastroesophageal reflux disease and vascular compression.

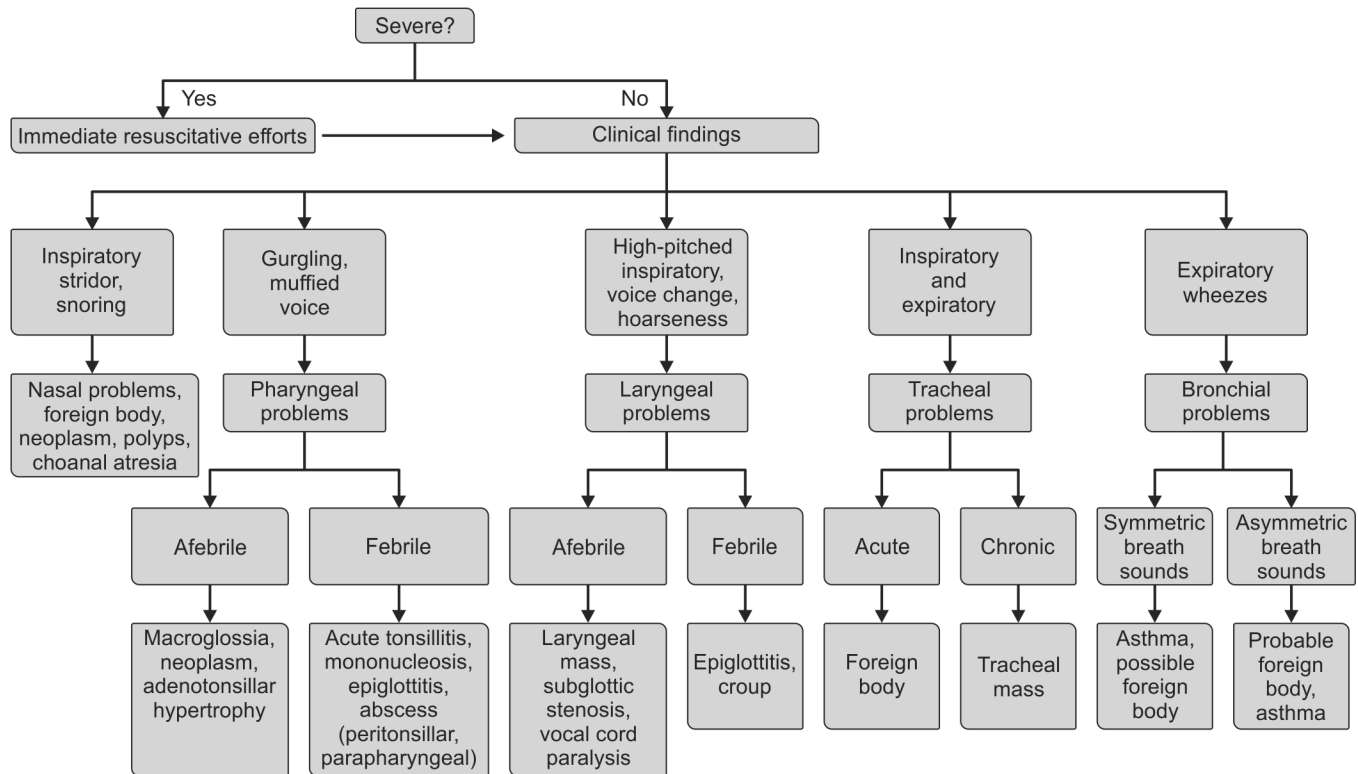
Common causes of stridor in children are croup, epiglottitis or foreign body. In foreign body aspiration, a preceding history of aspiration or choking can be obtained in majority of cases. If there is antecedent history of upper respiratory infection, croup, epiglottitis or tracheitis is a possibility. Drooling of saliva suggests epiglottitis or retropharyngeal and peritonsillar abscess. Barking cough is reported in croup, brassy cough in tracheitis; weak cry in neuromuscular disorder and laryngeal defects, hoarseness of voice in croup and vocal cord paralysis, and muffled cry and dysphagia in supraglottic lesions. If there is a history of endotracheal intubation, then suspect subglottic stenosis or vocal cord injury.

Investigations

Initial investigations include complete blood count and arterial blood gas (ABG) analysis to look for oxygenation and ventilation status. X-rays evaluation of the neck is useful in the initial assessment of airways. Look for adenoids, tonsils and epiglottic size and shape, retropharyngeal space and tracheal delineation. The lateral X-ray neck should be taken with neck extension to differentiate between retropharyngeal and pharyngeal masses. Contrast studies using barium or gastrografin should be used, if either vascular compression or gastroesophageal reflux disease or tracheoesophageal fistula is suspected. Direct visualization and evaluation of the airway using flexible fiberoptic bronchoscopy is often required in children with persistent stridor. CT or MRI is required to clarify the airway anatomy and the surrounding soft tissue structures, including vascular anomalies. If any vascular or structural heart lesion is suspected, an echocardiogram with Doppler may be done.

Table 1 Causes of stridor in newborn and children

Nose and pharynx	Larynx	Trachea
Choanal atresia	Laryngomalacia	Tracheomalacia
Lingual thyroid or thyroglossal cyst	Laryngeal web, cleft, cyst or laryngocele	Bacterial tracheitis
Macroglossia (e.g., Pierre-Robin sequence, Beckwith-Wiedemann syndrome)	Laryngotracheobronchitis (viral croup)	Congenital tracheal stenosis
Retrognathia (e.g., Treacher-Collins syndrome)	Acute spasmodic laryngitis (spasmodic croup)	External compression
Micrognathia (Treacher-Collins syndrome, Hallermann-Streiff syndrome)	Epiglottitis	
Hypertrophic tonsils/adenoids	Vocal cord paralysis	
Retropharyngeal or peritonsillar abscess	Laryngeal stenosis	
	Intubation	
Extrinsic compression	Foreign body	
Lymphatic malformations (cystic hygroma)	Cystic hygroma	
Vascular malformation (AV malformations)	Subglottic hemangioma	
Vascular tumors (hemangiomas)	Laryngeal papilloma	
Encephaloceles	Angioneurotic edema	
	Laryngospasm (hypocalcemic tetany)	
	Psychogenic stridor	

Flow chart 1 Approach to stridor in children

Adapted from Handler SD. Stridor. In: Fleisher GR, Ludwig S. Textbook of Pediatric Emergency Medicine. Baltimore: Williams and Wilkins; 1993. pp. 474-8.

Treatment

Treat the underlying cause. The establishment of airway patency is an emergency in children with severe respiratory distress or impending respiratory failure. Supportive management with oxygen, humidified air, intravenous fluids, steroids and β -adrenergic drugs may be required.

CROUP

Croup or laryngotracheobronchitis (LTB) is characterized by inspiratory stridor, barking cough and hoarseness of voice due to laryngeal and/or tracheal obstruction. The causative agent is most often a viral agent. In infants and children, viral croup is the most common cause of infective upper airway. In most of the cases, the disease has a mild and self-limited course.

Epidemiology

It usually affects in preschool age group with the peak incidence around 18-24 months. Infection is mainly airborne via droplet spread or direct inoculation through fomites. Epidemic can occur with parainfluenza viruses during winter months. In younger children, there is slight male preponderance (1.4:1), while in older age groups both sexes are equally affected.

Etiology

The most common etiologic agents are the parainfluenza viruses. Out of the three strains of parainfluenza viruses, type 1 is the most common causative agent and leads to epidemics. Other etiologic agents which can cause LTB include respiratory syncytial virus, coronavirus, influenza virus, metapneumovirus, adenovirus, rhinovirus and enterovirus. When croup is caused by herpes viruses, the clinical picture is usually more severe and protracted. However, the severity of symptom does not correlate with any particular infectious agent.

Pathogenesis

The incubation period of viral croup varies from 2 days to 6 days. Viral infection results in inflammation, edema of the airways and mucus production, which leads to narrowing of airways. Parainfluenza viruses are trophic for the respiratory epithelium, binding with the ciliated epithelium. Since the subglottic area is the narrowest part of a child's upper airway, with abundant mucous glands, it has a great propensity to become obstructed early. Also the negative intrathoracic pressure generated during inspiration tends to narrow the already inflamed and edematous airway; this further increases the airway obstruction. With the disease progression and production of fibrous exudates, the airways are further compromised. Vocal cord swelling produces hoarseness of voice. The barking cough is produced by the inflammation of the larynx and trachea.

Clinical Features

The initial phase is the prodromal phase which consists of rhinorrhea, pharyngitis, mild cough, and low-grade fever for 1-3 days. This is followed by characteristic *barking* cough, hoarseness of voice and inspiratory stridor. These symptoms are characteristically worse at night and are aggravated by agitation and crying; they often recur over several days with decreasing intensity.

Almost two-thirds children have mild symptoms which resolve within 2-5 days. With increasing severity of croup, the child will have signs and symptoms of respiratory distress, e.g., tachycardia, tachypnea, nasal flaring and use of accessory muscles of respiration (supraclavicular, infraclavicular, intercostal, subcostal and sternal retraction), persistent stridor and finally cyanosis (**Table 2**). Oxygen saturation may be well preserved until the late stages of severe croup, underestimating the respiratory compromise in a sick child who is receiving supplemental oxygen. Conversely, desaturation may be present with mild airway obstruction (lower

Table 2 Severity of croup

Signs/symptoms	Mild croup	Moderate croup	Severe croup
Stridor	Absent at rest	Present at rest	Continuous stridor
Respiratory distress	Nil	Chest wall retraction, tachypnea, use of accessory muscles of respiration	Marked distress, drooling, cyanosis
Sensorium	Playful, eats and drinks well	Less playful, interactive, take liquids orally	Anxious, tired, refuses liquids. Later becomes restless and agitated

airway involvement and ventilation perfusion mismatch). Late signs of airway obstruction are restlessness, agitation, cyanosis, pallor or decreased level of consciousness.

The most familiar scoring used for assessing severity of croup is the *Westley Croup Score*. Points are given according to the severity of symptoms. Mild croup has a score of less than or equal to 2, moderate disease has scores 3–7 and severe disease has scores of greater than or equal to 8. Scores above 12 are considered life-threatening and indicated impending respiratory failure (**Table 3**).

Investigations

Croup is a clinical diagnosis and does not require any laboratory tests. There is no role for radiography in assessment of acute airway obstruction. On the contrary, any unnecessary test will cause apprehension and increased agitation and crying, which might further increase the airway obstruction. The child should be kept calm and comfortable. Radiograph of the neck shows a typical subglottic narrowing *steeple sign* seen in croup (**Fig. 1**). However, this sign may be absent in some cases of croup and may

be seen as a normal variant also. Further evaluation is warranted when foreign body aspiration is suspected, doubtful diagnosis and unsatisfactory response to standard treatment. Additional studies, which might be required after the acute episode has resolved, include airway endoscopy, contrast assessment of upper airway, pH studies and polysomnography.

Differential Diagnosis

Viral croup needs to be differentiated from other infectious and noninfectious causes of stridor (**Table 4**). If a foreign body aspiration is suspected, history of recent aspiration or choking is usually present. A laryngotracheal *foreign body* presents with sudden onset cough, stridor and dyspnea, whereas bronchial foreign bodies present with cough, decreased breathe sounds and monophonic wheeze. *Epiglottitis* is a medical emergency in which the child appears toxic and presents with acute onset of high-grade fever, stridor, difficulty in swallowing and labored breathing. These children will drool and sit or lean forward with a hyperextended neck assuming a tripod position. There is no barking cough. In *bacterial tracheitis*, the initial clinical presentation is like viral croup, but the patient deteriorates with high fever, increasing respiratory distress and airway obstruction. Children have a toxic appearance and do not respond to the conventional treatment for viral croup. In *spasmodic croup*, the initial presentation is like LTB, but without any viral prodrome and fever. Spasmodic croup occurs commonly at night with sudden onset of barking cough, hoarseness, noisy respiration and respiratory distress, which usually diminishes in the morning. As part of anaphylaxis and allergic reactions, *angioneurotic edema* presents with sudden swelling of the face, tongue, laryngopharynx, stridor and respiratory difficulty. Rarely, *hypocalcemia* can present with tetany, irritability and stridor due to laryngospasm.

Table 3 Westley Croup Scoring System

Symptom	Score
<i>Level of consciousness</i>	
Normal (including sleep)	0
Disoriented	5
<i>Cyanosis</i>	
None	0
Cyanosis with agitation	4
Cyanosis at rest	5
<i>Stridor</i>	
None	0
When agitated	1
At rest	2
<i>Air entry</i>	
Normal	0
Decreased	1
Markedly decreased	2
<i>Retractions</i>	
None	0
Mild	1
Moderate	2
Severe	3

Adapted from Westley CR, Cotton EK, Brooks JG. Nebulized racemic epinephrine by IPPB for the treatment of croup: a double-blind study. *Am J Dis Child*.1978;132:484-7.

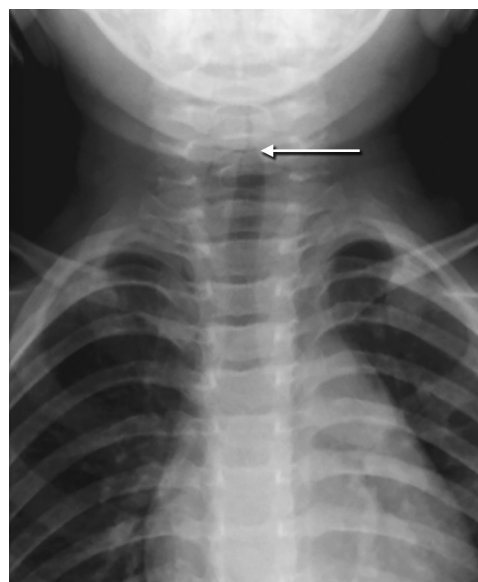
**Figure 1** Subglottic narrowing of trachea (arrow) *steeple sign*

Table 4 Differential diagnosis of croup

Infectious	Noninfectious
Croup (laryngotracheobronchitis)	Foreign body
Epiglottitis	Spasmodic croup
Bacterial tracheitis	Angioneurotic edema
Retropharyngeal abscess	Burns or thermal injuries
Peritonsillar abscess	Hypocalcemia
Diphtheria	Smoke inhalation
Infectious mononucleosis	

Management

Treatment of croup is based on clinical severity of the disease (**Tables 2 and 3**). Mild cases may resolve spontaneously without any medical intervention. If left untreated, moderate and severe cases can deteriorate and lead to respiratory failure. Utmost attention should be given to airway management and treatment of hypoxia.

Supportive Care

Mild cases can be managed at home, with plenty of fluids and antipyretics. Parents should be counseled about exacerbation of symptoms during night.

Humidity

Cochrane systematic review has concluded that humidification of air has no evidence and it is no longer recommended. Equipment that increases humidity can cause burn from boiling water and facial scald injuries.

Corticosteroids

Corticosteroids form the cornerstone of treatment for croup. The current evidence strongly supports their role in moderate and severe symptoms. The exact mechanism of action is unclear, although its anti-inflammatory property is thought to decrease the degree of inflammation and swelling in the airway. According to a recent Cochrane review (2012) which included 38 studies ($n = 4,299$), use of steroids was associated with an improved Westley score at 6 hours. At 24 hours, this improvement was no longer significant. The use of corticosteroids was associated with fewer return visits, readmissions, decreased hospital stay and decreased use of epinephrine. However, there are some issues including the optimal route of giving corticosteroids, dosing regimen and the best oral agent. Studies conclude that nebulized, oral and intramuscular routes are roughly equivalent. Nebulized route could possibly increase distress and increase airway obstruction, although it may be used in a child who is vomiting or having difficulty in swallowing. With oral administration, the fear and the discomfort of an injection are gone. The intramuscular route is preferable for children who are suffering from gastrointestinal symptoms.

Studies have used oral dexamethasone, prednisolone and nebulized budesonide. Dexamethasone has a potent anti-inflammatory activity compared to prednisolone and a longer half-life. Because of its long half-life (36–72 hours), one dose of dexamethasone suffices to cover the initial 72 hours period of the illness. The most widely used dosage of dexamethasone is 0.6 mg/kg administered as a single oral dose for the management of croup. Several studies have demonstrated that a dosage of 0.15 mg/kg is as effective (equivalent dose of prednisolone is 1 mg/kg). Oral dexamethasone is as effective as intramuscular dose. Nebulized budesonide has also equal efficacy as

dexamethasone. An improvement in croup symptoms is usually seen within 3–6 hours following corticosteroid administration. Prolonged use of dexamethasone is associated with development of *Candida albicans* laryngotracheitis.

Nebulized Epinephrine

It causes rapid reduction in airway edema and bronchodilation. It has a rapid onset of action (within 30 min), and the effect lasts for 2–3 hours. Both racemic and L-isomer are equally effective. It should be given in moderate and severe croup. The recommended dosage of epinephrine is 0.4–0.5 mL/kg (maximum dose is 5 mL) of 1:1000 preparations. Studies have shown that it decreases hospital admission and leads to improvement in the croup score.

Other Adjunctive Treatments

These include oxygen in a child with severe airway obstruction and hypoxia, and antipyretics or analgesics. According to a recent Cochrane review (2013), in moderate-to-severe croup who have received steroid, Heliox inhalation has some short-term benefits. Since it is a viral disease, antibiotics are not warranted. Antibiotics are only required for bacterial superinfection such as tracheitis, pharyngitis or pneumonia. Cough suppressants are not recommended for the treatment of croup.

Prevention

As croup is a transmissible viral respiratory disease, hand washing is of utmost importance. All people dealing with infected nasopharyngeal secretions should regularly wash their hands. Any potentially infected facial tissue is a potent infectious material and should be discarded immediately. Toys or other objects that have been mouthed by a child with croup should be washed. Visitors or relatives suffering from cold and cough should avoid proximity with children.

IN A NUTSHELL

1. Stridor is a harsh sound due to turbulent airflow through narrowed airways.
2. Presence of stridor requires urgent attention and thorough evaluation to delineate the underlying cause.
3. Croup is characterized by sudden onset of hoarseness, barking cough, stridor with or without the presence of respiratory distress.
4. Assess airway, breathing and circulation and focus on airway management.
5. Corticosteroids are the mainstay of treatment for croup.
6. For moderate, severe or life-threatening croup, add nebulized adrenaline.

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Chapter 39.14

Approach to a Child with Fast Breathing

Soumya Tiwari, Varinder Singh

Fast breathing is the most common presentation in children visiting a hospital emergency. It is defined as the respiratory rate more than the normal upper limit for that age group (**Table 1**). Fast breathing can be physiological, e.g., as a result of exercise, strenuous work or crying or due to fever, where the rate though increased may not reach the upper limits described. Fast breathing usually is a cardinal sign of respiratory disease but can result from nonrespiratory causes as well (**Box 1**). In certain pathological states due to underlying respiratory or nonrespiratory causes, fast breathing might be associated with increased work of breathing in the form of chest indrawing, nasal flaring and head nodding. It may also be associated with stridor or wheeze suggesting of upper and lower airway obstruction respectively.

There is a need for an urgent assessment of airway patency and breathing compromise when a child with fast breathing is first evaluated. Stabilization of vital parameters may require intubation, oronasal suctioning, use of oxygen by hood or nasal prongs, intravenous fluid boluses, correction of hypoglycemia, nebulization with bronchodilator, intercostal tube drainage, correction of hyperthermia or hypothermia, etc. Such initial treatment coupled with a thorough history, physical examination

and relevant investigations is followed by establishing a provisional diagnosis and instituting appropriate empirical treatment in the emergency ward itself.

CLINICAL FEATURES

A child with fast breathing may have respiratory symptoms such as cough, coryza or noisy breathing. Presence of fever suggests infectious etiology. In a child presenting with dyspnea on exertion or orthopnea, a cardiovascular etiology should be suspected. To assess the degree of respiratory compromise, one should assess for increased work of breathing (suggested by use of accessory muscles), cyanosis, lethargy or altered sensorium. Alteration in sensorium (in the form of irritability, agitation, lethargy or coma) indicates brain hypoxia and is one of the ominous indicators. A normal or decreased respiratory rate may also be ominous, if it is associated with severe retractions (paradoxical breathing), cyanosis, grunting or altered sensorium. Central cyanosis is a late sign but may not be detected in presence of severe pallor (severe anemia) and dark skin color.

Stridor is a harsh inspiratory sound that indicates upper airway obstruction. Grunt is a loud noise produced by a forceful expiration against a closed glottis. Grunt and wheeze (musical sound) are suggestive of lower respiratory tract involvement.

A complete history should reveal the onset, duration, progression of dyspnea, the aggravating and relieving factors as well as the associated symptoms such as fever, cough, sore throat, chest pain, choking episodes, accidental ingestion of poisons that may suggest the probable etiology (**Table 2**).

Symptoms of impending respiratory failure and red flag signs are listed in **Box 2**.

Table 1 The upper limits of respiratory rate as defined by the WHO

Age group	Respiratory rate cut-off
Young infant (< 2 months)	> 60/min
Infant (2 months to 1 year)	> 50/min
Toddlers and preschoolers (1–5 years)	> 40/min
School children (> 5 years)	> 30/min

Table 2 Clinical features suggestive of likely pathology for fast breathing

Clinical features	Diseases
Fever, cough and rapid breathing	Lower respiratory tract infections like pneumonia, bronchiolitis and virus-associated wheeze
Exercise-induced dyspnea	Asthma, CHF, severe anemia
Nocturnal cough, orthopnea and dyspnea	CHF
Fever, sore throat, stridor	Acute epiglottitis
Severe chest pain with rapid, shallow breathing, decreased air entry	Pneumonia, pneumothorax, pulmonary embolism
Persistent wheezing, recurrent vomiting, failure to thrive	GERD
Acute respiratory distress after sudden choking, hyperinflated chest	Foreign body inhalation
Fever with altered sensorium, convulsions, fast breathing	Encephalitis involving brainstem
Chest wall retractions, paraplegia	Acute flaccid paralysis
Acute respiratory distress with vomiting, altered sensorium	Hydrocarbon poisoning
Anuria, generalized edema, shock, anemia	Acute kidney injury/chronic kidney disease with metabolic acidosis
Fast breathing, altered sensorium, polyuria, dehydration	DKA

Abbreviations: CHF, congestive heart failure; GERD, gastroesophageal reflux disease; DKA, diabetic ketoacidosis.

BOX 1 Causes of fast breathing in children*Upper Respiratory Tract Involvement*

- Croup, acute epiglottitis, Ludwig angina
- Retropharyngeal abscess
- Foreign body aspiration
- Diphtheria
- Laryngospasm

Lower Respiratory Tract Involvement

- Pneumonia
- Bronchiolitis
- Asthma
- Pleural effusion, empyema and hemothorax
- Pneumothorax
- Atelectasis
- Hypersensitivity pneumonitis

Nonpulmonary Causes

- CHF due to heart disease or severe anemia
- CNS infections, cerebral edema, tumor (raised ICT, compression of the brainstem), spinal cord injury, Guillain-Barré syndrome
- Metabolic acidosis due renal failure, DKA, renal tubular acidosis, shock, lactic acidosis, etc.
- Psychogenic hyperventilation, anxiety, panic attacks

Abbreviations: CNS, central nervous system; CHF, congestive heart failure; DKA, diabetic ketoacidosis; ICT, intracranial tension.

BOX 2 Clinical pearls: warning signs in fast breathing*Symptoms of Impending Respiratory Failure*

- Cyanosis
- Silent chest
- Poor respiratory efforts
- Fatigue/exhaustion
- Agitation or reduced level of consciousness

Preterminal Signs

- Bradycardia
- Desaturation
- Altered sensorium

Red Flag Signs

- Respiratory rate (RR) ≥ 70 /min
- Severe chest indrawing
- Head nodding/grunting
- Central cyanosis
- Stridor in a calm child
- Inability to feed

INVESTIGATIONS

Laboratory investigations help to confirm the diagnosis, but the immediate management of a patient should not be delayed pending the reports of the investigations. Use of noninvasive devices such as pulse oximeter and end-tidal (ET) CO₂ detector (fitted in the ventilator) lessen the need for repeated invasive tests for monitoring of the child. **Table 3** shows the relevant investigations to ascertain the cause of fast breathing in a child.

MANAGEMENT

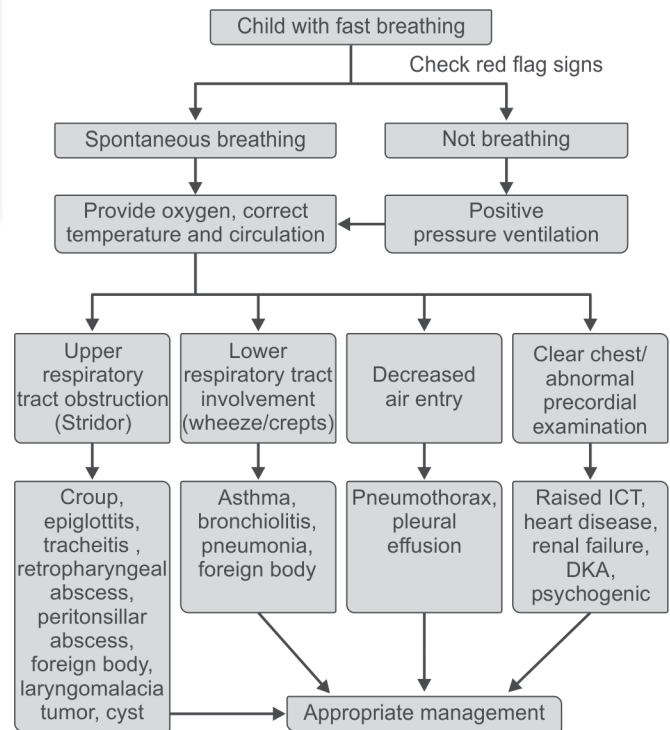
The management of a child with fast breathing includes supportive treatment in the form of stabilization of vital parameters, i.e.,

Table 3 Laboratory investigations in fast breathing

Investigation	Likely diagnosis
Complete blood count with peripheral smear: Leukocytosis/leukopenia, toxic granules, shift to left, low Hb, eosinophilia	Sepsis, anemia, tropical pulmonary eosinophilia
CRP, ESR: Raised	Sepsis, pneumonia, bronchiolitis
Blood culture	Sepsis with pneumonia
Kidney function tests: Deranged	Acute/chronic kidney disease
Arterial blood gas: Hypoxemia, hypercarbia, acidosis (metabolic/respiratory)	Severe pneumonia, pneumothorax, DKA, acute kidney injury, poisoning
Chest X-ray, X-ray soft tissue neck	Pneumonia, pneumothorax, pleural effusion, foreign body, acute epiglottitis, CHF
Bronchoscopy	Foreign body
Echocardiography	Cardiac disease
24 hours pH monitoring	GERD
Pleural tap	Pneumonia (bacterial, tubercular)
Lumbar puncture/cranial CT scan: Pleocytosis, raised protein and decreased sugar	Meningoencephalitis/raised ICT

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; DKA, diabetic ketoacidosis; CHF, congestive heart failure; GERD, gastroesophageal reflux disease; ICT, intracranial tension.

temperature, airway, breathing and circulation followed by definitive treatment by instituting appropriate respiratory support, antibiotics, chest tube drainage, decongestive measures, etc. Acute onset of fast breathing, especially following choking, and stridor indicate foreign body and warrant prompt bronchoscopic search and removal of foreign body (**Flow chart 1**).

Flow chart 1 Algorithmic approach to management of fast breathing

Abbreviations: DKA, diabetic ketoacidosis; ICT, intracranial tension.

IN A NUTSHELL

1. Fast breathing is one of the most common disease manifestations in sick infants and children.
2. It is important to promptly identify the cause of fast breathing based on the physical examination (pulmonary/nonpulmonary, upper respiratory/lower respiratory) and quickly manage those demonstrating the red flag signs (signs of nearly impending respiratory failure).
3. Supportive management should be instituted quickly, simultaneously searching for the etiology and planning a definitive treatment.

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Chapter 39.15

Approach to a Child with Wheeze

Soumya Tiwari, Varinder Singh

Wheezing is a common complaint in young children with respiratory disorders as it can occur in approximately one-third of children younger than 2 years of age with respiratory diseases. It is described as a continuous musical sound heard during chest auscultation. Although asthma is the most commonly encountered respiratory disorder in children presenting with wheeze, it may indicate a host of other illnesses such as gastroesophageal reflux, bronchiolitis or foreign body aspiration.

ETIOPATHOGENESIS

Wheeze is produced by oscillation of the airway walls when their lumen is severely compromised. Younger children (under 5 years of age) are more prone to wheezing due to several causes. As the resistance to airflow through a tube is inversely related to the fourth power of the tube's radius, smaller children can have wheeze with even a marginal narrowing of their airways. The higher compliance of the chest wall in younger children results in collapse of the intrathoracic airways due to the inward pressure produced in expiration. The airway compliance in younger children is further increased by the different tones of smooth muscle and cartilage rings of the trachea.

Wheezing has been associated with a variety of risk factors that include fetal malnutrition, maternal smoking, allergy, high infant adiposity and viral infections during infancy, the common viruses include respiratory syncytial virus (RSV), rhinovirus, cytomegalovirus and adenovirus.

Wheezing can be monophonic or polyphonic. Monophonic wheeze has a constant character on auscultation in all areas of the chest as it originates from large airway obstruction, while a polyphonic wheeze occurs due to small airway obstruction. Wheezing in infants is commonly produced by inflammation, but many other disease processes can also present with wheezing (**Box 1**).

HISTORY

Sudden onset of wheezing raises the possibility of foreign body aspiration, particularly, if there is a history of choking, while

an insidious increasing wheeze may be a sign of extraluminal compression of bronchi by an enlarged lymph node or growing mass. Persistent wheezing presenting very early in life suggests a structural or congenital problem; in contrast, paroxysmal or intermittent wheezing is a characteristic feature in asthma. Infrequently, the children with interstitial lung disease can present with persistent wheezing, particularly, those with postinfectious bronchiolitis obliterans.

Cough is almost always associated with wheezing. It may be dry or wet depending upon the underlying etiology; wet cough typically is seen in disorders with infection or inflammation (bronchiectasis, cystic fibrosis, primary ciliary dyskinesia and chronic aspiration) resulting from excessive mucus production and dry cough resulting from structural causes for airway narrowing (e.g., asthma, tracheo/bronchomalacia or compression, foreign body or vascular ring). However, the underlying etiology of a dry cough can be complicated by a secondary process (say an allergic or infective sinusitis), making this distinction less useful.

All that Wheezes is Not Asthma

Wheezing is almost considered synonymous with asthma, while there can be several different causes for wheezing. Clinical pointers favoring asthma as a cause of wheezing include episodic wheeze, triggered by upper respiratory infections, seasonal changes, exercise or allergens, particularly in those with a personal or family history of asthma and/or atopy. Such cases will usually have a good response to bronchodilators. On the other hand, clinical pointers favoring a diagnosis other than asthma are many (**Table 1**) including presence of a poor or unpredictable response to bronchodilators, premature babies, particularly, those needing resuscitation or prolonged oxygen or ventilator support, wheezing since birth (congenital abnormality), wheezing associated with feeding or vomiting and presence of clubbing. History of choking, especially with associated coughing or shortness of breath, suggests foreign body aspiration, even if it does not immediately precede onset of wheezing symptoms. Past history of recurrent respiratory tract infections, malabsorption, failure to thrive, poor weight gain and recurrent ear or sinus infections suggest cystic fibrosis, immunodeficiency or ciliary dysfunction. History of progressive dyspnea, tachypnea, exercise intolerance and failure to thrive suggest interstitial lung disease.

PHYSICAL EXAMINATION

The physical examination should include anthropometry, vital parameters including oxygen saturation and inspection for the presence of cyanosis or clubbing. Nasal examination may reveal signs of allergic rhinitis, sinusitis or nasal polyps; the presence of nasal polyps in children necessitates an evaluation for cystic fibrosis.

A detailed chest examination will give clues to the etiology as well as the severity of the disease. Presence of respiratory distress—tachypnea, retractions, signs of hyperinflation such as increased anteroposterior (AP) diameter, Harrison sulcus suggests persistent and/or severe disease. On auscultation, one may hear typical wheeze or in milder instances a prolonged expiratory phase. The presence of focal wheezing is usually indicative of a localized and mostly structural airway abnormality and may warrant further airway evaluation by imaging or bronchoscopy.

Creptations can be present in conjunction with wheezing in asthma and in a variety of other conditions such as those leading to bronchiectasis (e.g., cystic fibrosis, primary ciliary dyskinesia, immune deficiency). Early inspiratory crepts are often present in patients with asthma due to air flowing through secretions or slightly closed airways during inspiration. Late inspiratory crepts are usually associated with early congestive heart failure or interstitial lung disease.

BOX 1 Common causes of wheezing in children

Infection

- *Viral*: Respiratory syncytial virus, parainfluenza virus, adenovirus, influenza virus, rhinovirus.
- *Other infections*: *Chlamydia trachomatis*, tuberculosis, histoplasmosis, papillomatosis.

Asthma

Anatomical Abnormalities

- *Central airway*: Airway malacia, tracheoesophageal fistula (H-type fistula), laryngeal cleft.
- *Extrinsic airway anomalies*: Vascular ring, extrinsic compression by tumor, lymph node or foreign body in esophagus.
- *Intrinsic airway anomalies*: Airway hemangioma, bronchial or lung cyst, congenital lobar emphysema, foreign body.

Others

Gastroesophageal reflux, AIDS, cystic fibrosis, bronchiectasis, burns, interstitial lung diseases.

Table 1 Clinical pointers favoring a diagnosis other than asthma

<i>Atypical features suggesting alternative diagnoses</i>	<i>Consider/Investigate for</i>
1. Onset below 6 months of age	
a. Choking episodes, vomiting, symptoms related to feeds	Aspiration syndromes, e.g., GERD
b. Short prodrome of cough, coryza, wheeze	Bronchiolitis
c. Persistent wheeze/stridor, cardiac failure, cyanosis, murmur	Vascular slings or left to right shunts
2. Persistent respiratory symptoms	
a. Persistent cough, upper airway symptoms, fever	Adenotonsillitis, sinusitis
b. Persistent cough, constitutional symptoms, tuberculosis contact, adenopathy	Tuberculosis
3. Unusual symptoms	
a. Recurrent multifocal bacterial infections including respiratory infections	Immunodeficiency states, (as suggested by SPUR*)
b. Recurrent respiratory symptoms, clubbing, coarse crepitations \pm dextrocardia, situs inversus	Ciliary dyskinesia
c. Recurrent respiratory symptoms, consanguinity, malabsorption, failure to thrive	Cystic fibrosis
4. First life-threatening episode	
a. History suggestive of foreign body inhalation, localized wheeze, unequal air entry	Foreign body
b. History suggestive of diet allergy	Food allergy

*SPUR: Severe, Persistent, Unusual, Recurrent infections.

(From: ABC, Asthma by Consensus, IAP guidelines on asthma management)

INVESTIGATIONS

A chest radiograph (AP and lateral films) should be considered in children with new-onset wheeze of undetermined origin or chronic persistent wheezing not responding to treatment. The presence of generalized hyperinflation suggests diffuse airtrapping (cystic fibrosis, asthma, primary ciliary dyskinesia and tracheal foreign body). A chest radiograph can also detect parenchymal lung disease, atelectasis, bronchiectasis or extraluminal compression by lymph node, tumor. In addition, chest radiographs may reveal cardiomegaly, enlarged pulmonary vessels, pulmonary edema or other signs of cardiac failure. Barium swallow may help in identifying vascular rings, swallowing dysfunction, aspiration syndromes including gastroesophageal reflux and some cases of tracheoesophageal fistula.

Pulmonary function tests (PFTs) are important component of the diagnostic evaluation of a wheezy child. In older children who are cooperative, pulmonary function testing is helpful in determining the presence, degree and location of airway obstruction as well as the response to bronchodilators.

Complete blood count may show eosinophilia, suggesting an underlying allergic process or possible parasitic infection. Elevated IgE can be indicative of an allergic process. Tests for cystic fibrosis (sweat chloride test or mutation analysis) or for immunodeficiencies are needed when clinical clues suggest these diagnoses. Flexible bronchoscopy may be needed to rule out airway malacia, foreign body aspiration or other causes of intraluminal or extraluminal obstructions which can present as persistent and/or localized wheeze.

MANAGEMENT

Treatment depends on the underlying cause; however, the first and foremost is establishing airway and breathing and maintaining oxygenation. Presence of severe respiratory distress warrants hospitalization.

Response to initial bronchodilator therapy suggests a component of bronchial hyper-reactivity. For children less than 3 years of age with demonstrable therapeutic benefit, the inhaled medications can be administered through a metered-dose inhaler (MDI) with mask and spacer. Inhalation therapy should be continued in all patients with viral-induced asthma exacerbation.

Ipratropium bromide is effective as an adjunct therapy, especially in children with significant tracheal and bronchial

malacia. Children with tracheomalacia or bronchomalacia may worsen with use of β_2 -agonists.

A trial of inhaled steroids may be considered in a child with previous response to oral steroids and who has moderate-to-severe wheezing, a significant past history of atopy, or a family history of asthma or atopy. Inhaled corticosteroids are indicated for long-term maintenance therapy in children with known airway reactivity but are controversial when used for episodic viral or acute illnesses. Intermittent, high-dose inhaled corticosteroids are not recommended for intermittent wheezing. Early use of inhaled corticosteroids has not been shown to prevent the progression of childhood wheezing or affect the natural history of asthma in children (for more details see Chapter on Childhood Asthma).

Use of steroids in first-time wheezers or infants without hospitalization is controversial. Steroids are generally reserved for infants with atopic wheezing, who are thought to have asthma that is refractory to other medications.

In cases of inhaled foreign body, the bronchoscopic removal may result in a dramatic improvement in symptoms.

IN A NUTSHELL

1. Wheezing is a common presenting symptom of respiratory disease in children.
2. It may represent either a self-limited or benign process or alternatively may be a sign of significant respiratory disease.
3. Bronchial asthma is most likely diagnosis in children with recurrent wheezing.
4. Anteroposterior and lateral chest radiographs are indicated in children with new-onset wheezing of undetermined etiology or chronic persistent wheezing unresponsive to therapies.

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Chapter 39.16

Bronchiolitis

Ilin Kinimi

Bronchiolitis is a lower respiratory tract viral infection that primarily affects the small airways (bronchioles). It is defined as a clinical syndrome that occurs in children less than 2 years of age and is characterized by upper respiratory symptoms (e.g., rhinorrhea) followed by lower respiratory infection with inflammation, which results in wheezing and/or crackles (rales). Bronchiolitis typically occurs with primary infection or reinfection with a viral pathogen. In young children, the clinical diagnosis of bronchiolitis may overlap with recurrent virus-induced wheezing and acute viral-triggered asthma.

For clinical research, bronchiolitis is typically defined as the first episode of wheezing in a child younger than 12–24 months who has physical findings of a viral lower respiratory infection and no other explanation for the wheezing.

EPIDEMIOLOGY

Bronchiolitis typically affects infants and children younger than 2 years, principally during the fall and winter. Bronchiolitis hospitalization has a peak incidence between 2 months and 6 months of age and remains a significant cause of respiratory disease during the first 2 years of life and a leading cause of hospitalization in infants and young children.

In Indian studies, respiratory syncytial virus (RSV) infection was diagnosed in 30–70% of children with bronchiolitis. In a prospective hospital-based study from Southern India, of 114 children with bronchiolitis, 87 (76%) were less than 1 year and 107 (94%) were less than 2 years of age. Bronchiolitis occurs in epidemics during winter months. Outbreaks occur from September to March in India.

ETIOPATHOGENESIS

Bronchiolitis is typically caused by a viral infection. Although the proportion of disease caused by specific viruses varies depending upon the season and the year, RSV is the most common cause followed by rhinovirus. Less common causes include parainfluenza virus, human metapneumovirus, influenza virus, adenovirus, coronavirus and human bocavirus. With molecular diagnostics, two or more viruses are detected in approximately one-third of young children hospitalized with bronchiolitis. The virus typically infects the terminal bronchiolar epithelial cells causing direct damage and inflammation in the small bronchi and bronchioles. Edema, excessive mucus, and sloughed epithelial cells lead to obstruction of small airways and atelectasis.

CLINICAL FEATURES

Children typically present for medical attention 3–6 days after the onset of illness. Bronchiolitis often is preceded by a 1–3 days history of upper respiratory tract symptoms, such as nasal congestion and/or discharge and mild cough. It typically presents with fever (usually $\leq 38.3^{\circ}\text{C}$), cough and mild respiratory distress (e.g., mildly increased respiratory rate, mild retractions). Compared with other viruses that cause bronchiolitis, fever tends to be lower in RSV and higher with adenovirus infections.

Characteristic examination findings include tachypnea, mild intercostal and subcostal retractions, and expiratory wheezing. Additional auscultatory findings may include prolonged expiratory phase and coarse or fine crackles (rales). The chest may appear

hyperexpanded with increased anteroposterior diameter and may be hyper-resonant to percussion. Mild hypoxemia ($\text{SpO}_2 < 95\%$) is common. Other findings may include mild conjunctivitis, pharyngitis and acute otitis media.

Severely affected patients have increased work of breathing (subcostal, intercostal and supraclavicular retractions; nasal flaring and expiratory grunting). They may appear cyanotic and have poor peripheral perfusion. Wheezing may not be audible if the airways are profoundly narrowed or when increased work of breathing results in exhaustion. Serious comorbid infection is rare in children with bronchiolitis.

COMPLICATIONS

In most previously healthy infants, bronchiolitis resolves without complications. However, severely affected patients, particularly those with risk factors (**Box 1**) and those who require mechanical ventilation for apnea or respiratory failure, may develop air leaks including pneumothorax or pneumomediastinum. Bronchiolitis may be complicated by apnea, particularly in infants born prematurely and those less than 2 months of age. Presenting with apnea is a risk factor for respiratory failure and the need for mechanical ventilation. Respiratory failure is another serious complication of bronchiolitis.

BOX 1 Risk factors for severe bronchiolitis

- Prematurity (gestational age < 37 weeks)
- Age < 12 weeks
- Chronic pulmonary disease, particularly bronchopulmonary dysplasia (BPD)
- Congenital/anatomic defects of the airways
- Congenital heart disease
- Immunodeficiency
- Neurologic disease.
- *Environmental and other risk factors:* Passive smoking, crowded household, daycare attendance, concurrent birth siblings, older siblings and high altitude (> 2500 m).

DIAGNOSIS

Bronchiolitis is diagnosed clinically. Characteristic features include a viral upper respiratory prodrome followed by increased respiratory effort and wheezing and/or rales. Chest radiographs and laboratory studies are not necessary to make the diagnosis of bronchiolitis. However, they may support the diagnosis and may be necessary to either assess the severity or evaluate potential complications or exclude other conditions in the differential diagnosis.

Differential Diagnosis

Bronchiolitis needs to be differentiated from wheeze associated lower respiratory tract infections (LRTIs), pneumonia, aspiration pneumonia, congenital heart disease with failure, foreign body aspiration and chronic pulmonary disease. Differentiating points are highlighted in **Table 1**. Severe bronchiolitis also can unmask underlying airway obstruction that existed before the infection (e.g., vascular ring). Clinical features (e.g., lack of preceding upper respiratory tract symptoms, witnessed episode of choking, differential aeration and poor growth) may help to distinguish some of these conditions from bronchiolitis; for others, radiographic or laboratory studies may be necessary.

LABORATORY EVALUATION

Bronchiolitis is largely a clinical diagnosis. Laboratory tests are not routinely indicated in the evaluation of infants and young children with suspected bronchiolitis but may be needed when the diagnosis

Table 1 Differential diagnoses of bronchiolitis

Wheeze associated with LRTIs or multi-trigger wheeze	<ul style="list-style-type: none"> History of recurrent wheezing episodes, a family or personal history of asthma, eczema, and atopy help to support a diagnosis of asthma. However, during the first episode of wheezing, it is difficult to distinguish bronchiolitis from asthma.
Pneumonia	Symptoms and signs of both conditions are nonspecific; children with bacterial pneumonia may be more ill-appearing (e.g., higher fever), but clinical features cannot reliably differentiate bacterial LRTI from viral LRTI.
Foreign body aspiration	<ul style="list-style-type: none"> History of choking (not always present), focal monophonic wheezing, decreased air entry or regional variation in aeration. A high index of suspicion should be maintained for foreign body aspiration.
Chronic pulmonary disease	<ul style="list-style-type: none"> Suspected in children with prolonged or recurrent symptoms such as recurrent wheezing, failure to thrive, recurrent aspiration, stridor or recurrent respiratory infection. Children with underlying pulmonary disease may have a superimposed acute episode of bronchiolitis, and in some cases, the underlying disorder is unrecognized before the acute episode. Clinical course of bronchiolitis in children with underlying pulmonary disorders tends to be severe/require prolonged hospitalization.
Aspiration pneumonia	<ul style="list-style-type: none"> Secondary to GERD and/or swallowing dysfunction. May occur as a complication of bronchiolitis; the risk of aspiration increases during active bronchiolitis and resolves weeks later as tachypnea and the work of breathing subside. Clinical features associated with aspiration may include coughing with feeds, weak suck reflex and cyanosis during feeding and recurrent or chronic stridor.
Congenital heart disease	<ul style="list-style-type: none"> Associated findings may include failure to thrive, poor peripheral perfusion, abnormalities on cardiac examination (e.g., pathologic heart murmur, abnormal S₂, gallop, rub, active precordium). Children with underlying cardiac conditions may have a superimposed acute episode of bronchiolitis and in some cases the underlying disorder is unrecognized before the acute episode. Clinical course of bronchiolitis in children with underlying cardiac disorders tends to be severe/require prolonged hospitalization.
Heart failure	Associated clinical findings may include exercise intolerance, easy fatigue, hepatomegaly, shortness of breath, peripheral edema.
Vascular ring	<ul style="list-style-type: none"> Although stridor is more common, children with vascular rings may also have wheezing (typically with pulmonary artery slings). Anterior bowing of the trachea in the lateral chest radiograph may be a clue, but other modalities (barium contrast esophagogram, bronchoscopy, magnetic resonance angiography) usually are necessary for definitive diagnosis.

Abbreviations: LRTIs, lower respiratory tract infections; GERD, gastroesophageal reflux disease; S₂, second heart sound.

is in doubt. Data demonstrating the utility of complete blood counts (CBCs) in the diagnosis or management of bronchiolitis are lacking. However, laboratory and/or radiographic evaluation may be necessary to evaluate the possibility of comorbid or secondary bacterial infection in the following groups of patients:

- Neonates less than or equal to 28 days of age with fever [temperature $\geq 38^{\circ}\text{C}$ (100.4°F)] and symptoms and signs of bronchiolitis have the same risk for serious bacterial infection as young febrile infants without bronchiolitis.
- *Infants 28–90 days of age with fever:* CBC, urinalysis, urine culture and chest radiograph may be warranted to exclude comorbid or secondary bacterial infection in febrile [$T \geq 38^{\circ}\text{C}$ (100.4°F)] infants with symptoms and signs of bronchiolitis
- Children of any age with unusual or severe course (e.g., failure to improve after 2–5 days, wheezing that persists for > 7 days): CBC and chest radiograph may be warranted to evaluate secondary bacterial infection and other conditions in the differential diagnosis.
- *Children of any age with severe disease:* Arterial or capillary blood gas measurements may be necessary to evaluate respiratory failure.

Chest Radiography

It is not routinely indicated in the evaluation of infants and children with bronchiolitis as radiographic abnormalities are variable and nonspecific. Common findings include hyperinflation and peribronchial thickening. Patchy atelectasis with volume loss may result from airway narrowing and mucus plugging. Radiographic findings are poor indicators of the etiologic diagnosis and must

be used in conjunction with other clinical features in making decisions about diagnosis and treatment.

Virologic Studies

Virologic studies are not routinely required for specific viral agents unless the results will alter management of either patient or patient's contacts (e.g., initiation or continuation/discontinuation of antibiotic therapy, anti-influenza therapy, anti-influenza prophylaxis for high-risk contacts or cohorting of hospitalized patients or caregivers). The identification of a viral etiologic agent may be associated with a decreased utilization of antibiotic treatment and may help to avoid nosocomial transmission. However, direct evidence that this strategy prevents nosocomial transmission of respiratory viruses in children is lacking and it may be more logical to isolate all infants with bronchiolitis.

The recommended approach is screening by antigen detection or immunofluorescence of respiratory secretions obtained by nasal wash or nasal aspirate (rather than nasopharyngeal swabs). Nasal wash specimens are obtained by holding the infant or child upright at a 45° angle. A bulb syringe or a soft plastic catheter attached to suction is used to aspirate nasal secretions after a small amount of normal saline (1–3 mL) is instilled in each nostril. Rapid antigen tests are available for RSV, parainfluenza, adenovirus and influenza viruses. Culture and polymerase chain reaction (PCR) are additional methods that can be used. The sensitivity of most rapid antigen tests ranges from 80% to 90%. Given the little benefit these tests provide to the patient management, none of these is currently in use for routine clinical management of bronchiolitis in our country.

MANAGEMENT

Children can be managed as outpatients if they are adequately hydrated and have no signs of moderate to severe respiratory distress (e.g., nasal flaring, retractions, grunting, respiratory rate > 70 breaths/min, dyspnea or cyanosis) and do not require supplemental oxygen. Infants with bronchiolitis, who are not hospitalized, should be monitored in the outpatient setting by their clinician for progression of disease.

Assessing the Severity

Hospitalization for supportive care and monitoring is indicated depending on the severity of illness. Aspects of the history that help in determining the severity of illness and/or need for hospitalization are outlined in **Box 2**. Repeated observations are necessary to adequately assess the disease severity because examination findings may vary substantially over time. However, there is limited and/or conflicting evidence relating these clinical findings to clinical outcomes.

BOX 2 Assessment of severity of bronchiolitis

- Assessment of hydration status (e.g., fluid intake, urine output)
- Symptoms of respiratory distress (tachypnea, nasal flaring, retractions, grunting, $\text{SpO}_2 < 95\%$ on room air, respiratory rate ≥ 70 breaths/min)
- Cyanosis/toxic or ill appearance
- Episodes of restlessness/lethargy (may indicate hypoxemia/impending respiratory failure)
- A history of apnea with cyanosis or bradycardia
- Assessment of hydration status (e.g., fluid intake, urine output).

Several scores have been developed to assess the clinical severity of bronchiolitis in research settings, but these measures in clinical practice are limited by substantial variability in severity assessment between observers. The need for intensive care depends on the presence and type of risk factors (**Box 1**) for serious disease. Children with congenital heart disease, bronchopulmonary dysplasia (BPD), immunosuppression or those less than 6 weeks of age have up to 40% higher risk of requiring intensive care and thus need active and frequent monitoring.

Hypoxemia

It is associated with mucus plugging and atelectasis and is common in children with bronchiolitis. It may respond to supplemental oxygen alone, although sometimes it requires additional respiratory support. Hypercapnic respiratory failure, associated with fatigue, usually requires additional respiratory support (e.g., intubation and mechanical ventilation).

Secondary Bacterial Infection

With the exception of otitis media, secondary bacterial infection is uncommon among infants and young children with bronchiolitis or RSV infection. The risk of secondary bacterial pneumonia is increased among children who require admission to the intensive care unit, particularly those who require intubation. Routine use of antibiotics is therefore not recommended to prevent secondary bacterial infection.

Anticipatory Guidance and Supportive Measures

In healthy infants and young children, bronchiolitis usually is a self-limited disease. Management in most cases consists of anticipatory guidance and supportive measures to maintain oxygenation and hydration. However, bronchodilator therapy may be beneficial in a subset of patients.

Anticipatory Guidance

Education and anticipatory guidance are important components of the management which includes the expected clinical course; proper techniques for suctioning the nose; explaining the indications to return to medical care: apnea, cyanosis, poor feeding, fever, increased respiratory rate and/or work of breathing (retractions, nasal flaring, grunting); and stressing on the strategies to prevent respiratory infection.

Supportive Care

Supportive care includes maintenance of adequate hydration, provision of respiratory support as necessary and monitoring for disease progression (**Fig. 1**).

Fluids

Children with bronchiolitis may have difficulty in maintaining adequate hydration because of increased needs (related to fever and tachypnea) and decreased intake (related to tachypnea and respiratory distress). Exclusive parenteral fluid administration may be necessary to ensure adequate hydration and avoid the risk of aspiration in infants and children who are hospitalized with bronchiolitis and have moderate to severe respiratory distress. For children who can tolerate enteral feedings, strategies to maintain hydration include small frequent feedings or orogastric or nasogastric feedings.

Plasma antidiuretic hormone levels rarely may be elevated, leading to fluid retention and hyponatremia. Administration of hypotonic intravenous fluids may contribute to mild hyponatremia in some infants without affecting clinical improvement. Fluid overload should be avoided since it may lead to pulmonary congestion.

Nasal Congestion

Saline nose drops and nasal bulb suction may help to relieve partial nasal obstruction. There is little evidence to support routine *deep* suctioning of the lower pharynx or larynx in the inpatient setting.

Medications

Drugs used for the management of bronchiolitis are summarized in **Table 2**.

Inhaled Bronchodilators

Children with bronchiolitis with moderate to severe respiratory distress should receive a trial of inhaled bronchodilators. However, the efficacy of these medications remains uncertain. In a meta-analysis of 28 trials comparing bronchodilators other than

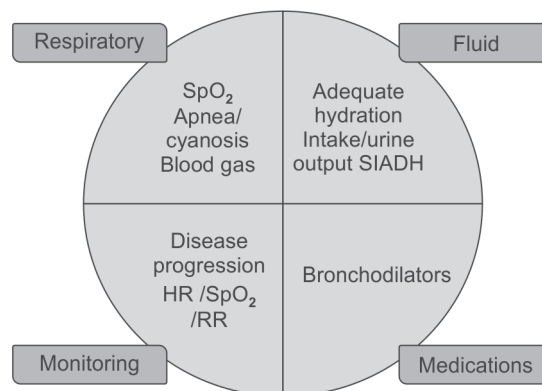


Figure 1 Components of management of bronchiolitis
Abbreviations: HR, heart rate; RR, respiratory rate.

Table 2 Drug treatment for bronchiolitis

	<i>Recommendations or evidence</i>	<i>Additional remarks</i>
Inhaled bronchodilators	Evaluate the child before and up to 1 hour after treatment. Administered with normal (0.9%) saline and with oxygen. Monitored trial of bronchodilator medication is an option, with continuation only if there is a documented objective clinical response.	Administer nebulized epinephrine (0.05 mL/kg of 2.25% epinephrine in 3 mL normal saline). Continue 4–6 hourly until discharge among those who show response.
Systemic steroids	First episode of bronchiolitis—not recommended	The use of glucocorticoids in hospitalized infants with BPD and those with multi-trigger wheeze (personal or family history of atopy) may be warranted.
Bronchodilators plus steroids	Not recommended	
Oral bronchodilators	Not recommended	Oral bronchodilators have neither shortened clinical illness / improved clinical parameters but are associated with adverse effects (increased heart rate). May be used after discharge in those showing response to initial bronchodilator therapy.
Hypertonic saline	Not recommended	
Antibiotics	Not recommended	Warranted only when there is evidence of a coexisting bacterial infection (e.g., positive urine or blood culture, AOM, consolidation on chest radiograph).
Ribavirin	Not recommended	However, in immunocompromised patients and those with severe RSV bronchiolitis, antiviral therapy may play a role.
Anti-RSV preparations	Not recommended	RSV-specific humanized monoclonal antibody (palivizumab) has failed to improve outcomes in infants (with or without risk factors) hospitalized with RSV infection.
Surfactant	Not recommended	However, additional data are needed before reliable estimates of the magnitude of the effects can be made.
Heliox	Not recommended	Administration of heliox is cumbersome and results in a relatively small benefit in a limited group of infants.

Abbreviations: AOM, acute otitis media; RSV, respiratory syncytial virus.

epinephrine with placebo, there were no significant differences in clinical score, oxygenation, hospitalization rate or duration of hospitalization. Another meta-analysis of 19 trials compared nebulized epinephrine with placebo or other bronchodilators. Compared with placebo, epinephrine decreased admissions within 24 hours of administration and was associated with short-term clinical improvements but did not affect admissions within 1 week or length of stay. Compared with salbutamol, epinephrine was associated with short-term clinical improvements but did not affect admission rate. Although epinephrine was associated with decreased length of stay compared with salbutamol, epinephrine did not decrease length of stay when compared with placebo. In a subsequent multicenter randomized trial comparing nebulized epinephrine with nebulized saline in infants (< 12 months) with moderate to severe acute bronchiolitis, length of stay, use of supplemental oxygen, ventilatory support nasogastric tube feeding and improvement in clinical score compared with baseline were similar between groups.

However, a monitored trial of bronchodilator medication is an option with continuation only if there is a documented objective clinical response.

Systemic Glucocorticoids

The anti-inflammatory effects of glucocorticoids are thought to reduce airway obstruction by decreasing bronchiolar swelling. However, most studies show little effect in bronchiolitis. A 2013 meta-analysis evaluating the use of systemic glucocorticoids for acute bronchiolitis in children (0–24 months of age) included 17 trials with 2,596 patients. In pooled analyses, no significant differences were found in hospital admission rate, length of stay, clinical score after 12 hours or hospital readmission rate. Whether glucocorticoids provide

benefit in different subgroups of children with bronchiolitis is uncertain. Some patients presenting the first episode of bronchiolitis may be experiencing inflammation from asthma and these patients can benefit from systemic glucocorticoids. Although patients with asthma can benefit from glucocorticoids, randomized controlled trials have demonstrated no benefit of oral glucocorticoids in young children with virus-associated wheezing. Another meta-analysis of three studies evaluating the use of systemic glucocorticoids in infants with bronchiolitis requiring admission to the intensive care unit found no overall effect on duration of mechanical ventilation or length of hospitalization.

Bronchodilators Plus Glucocorticoids

The possibility of synergy between bronchodilators and glucocorticoids has been evaluated in systematic reviews and meta-analyses. In one multicenter trial, 800 infants presenting to the emergency department (ED) with bronchiolitis were randomly assigned to one of four treatment groups: (i) nebulized epinephrine and oral placebo, (ii) oral dexamethasone and inhaled placebo, (iii) nebulized epinephrine and oral dexamethasone and (iv) nebulized and oral placebo. Outcomes in the dexamethasone and epinephrine monotherapy groups did not differ significantly from those in the placebo group. Treatment with dexamethasone and epinephrine was associated with a decreased rate of hospitalization within 1 week of the ED visit (17 vs 24–26% in the other groups), but the result was not significant when adjusted for multiple comparisons. The rate of hospitalization was not affected by RSV status, personal or family history of atopy, time of presentation or illness severity. The current data do not support combination bronchodilator-glucocorticoid therapy for children with bronchiolitis.

Nebulized Hypertonic Saline

Nebulized hypertonic saline theoretically has the potential to reduce airway edema and mucus plugging, the predominant pathologic features of acute bronchiolitis. A 2013 meta-analysis evaluating nebulized hypertonic saline for bronchiolitis in infants included 11 trials (1,090 patients). In pooled analysis of four trials (380 patients), treatment with 3% or 5% vs 0.9% saline (administered with bronchodilators) was associated with a nonsignificant reduction in hospitalization. Subsequent randomized trials comparing nebulized hypertonic (3% or 7%) and normal (0.9%) saline administered in the ED found mixed results with respect to hospitalization, but no benefit for clinical improvement or length of stay.

Respiratory Support

- **Supplemental oxygen:** It should be provided by nasal cannula, face mask or head box to maintain SpO₂ above 90–92%. Oxygenation by most nonthreatening fashion for delivery of oxygen. Sometimes less efficient and less predictable method like blow by method may be needed initially in a very irritable child. Persisting hypoxemia despite high oxygen flow, with or without severe distress, requires immediate assessment for ventilator assistance. Close monitoring is required as supplemental oxygen is weaned, particularly for children with hemodynamically significant heart disease, bronchopulmonary dysplasia and premature birth. During recovery phase, SpO₂ of 90–92% is accepted, if baby is feeding well and not distressed as sufficient for cessation of oxygen (except in infants with underlying chronic lung disease) and consider discharge.
- **Other measures:** Infants with arterial carbon or capillary dioxide tension more than 55 mm Hg, hypoxemia despite oxygen supplementation and/or apnea may require mechanical ventilation.
- **Continuous positive airway pressure (CPAP):** CPAP with or without helium-oxygen blends has gained favor as a way to decrease work of breathing and prevent endotracheal intubation in children with progressive hypoxemia or hypercarbia. However, additional studies are necessary to clarify the benefits of CPAP.
- **Heated, humidified high-flow nasal cannula therapy (HFNC):** HFNC is a noninvasive well-tolerated method of ventilatory support that permits high inspired gas flows (1–8 L/min) with or without increased oxygen concentration. Currently, there is insufficient evidence to determine the effectiveness of HFNC for treating bronchiolitis in infants. Additional trials are being conducted to determine the effectiveness and effect of various flow rates on airway pressure, breathing patterns and respiratory effort in infants hospitalized with bronchiolitis. Flow rates of more than or equal to 6 L/min (2 L/kg/min) appear to provide positive pressure throughout the respiratory cycle.

Monitoring

Repeated clinical assessment of the respiratory system (respiratory rate, nasal flaring, retractions and grunting) is necessary to identify deteriorating respiratory status in both the outpatient and inpatient settings. Early in the admission, hospitalized infants should have continuous monitoring of heart rate, respiratory rate and SpO₂. Infants with severe distress or who have apnea should be monitored in the intensive care unit. An arterial or capillary blood gas measurement may be indicated in children who require intensive care. A change from continuous to intermittent measurement of SpO₂ may be instituted as the clinical course improves.

Chest Physiotherapy

It is not recommended in the management of acute episode of bronchiolitis. A systematic review concluded that chest

physiotherapy using vibration and percussion or passive expiratory techniques did not improve respiratory parameters, reduce supplemental oxygen requirement or reduce length of hospital stay. The use of chest physiotherapy is discouraged because it may increase the distress and irritability of ill infants.

Minimal clinical criteria for discharge from the hospital, ED or office are listed in **Box 3**.

BOX 3 Discharge criteria for bronchiolitis

- Patient is stable without for bronchiolitis supplemental oxygen for at least 10–12 hours prior to discharge
- Patient has adequate oral intake to prevent dehydration
- The resources at home are adequate to support the use of any necessary home therapies (e.g., inhalation therapy if the trial was successful and this therapy is to be continued)
- Education of the family is complete.

CLINICAL COURSE AND PROGNOSIS

Typical illness with bronchiolitis begins with upper respiratory tract symptoms, followed by lower respiratory tract signs and symptoms on days 2–3, which peaks on days 5–7 and then gradually resolves. The duration of the illness due to bronchiolitis depends upon age, severity of illness, associated high-risk conditions and the causative agent. Bronchiolitis usually is a self-limited disease. Most children who do not require hospitalization recover by 2–8 days.

In previously healthy infants older than 6 months who require hospitalization, the average length of hospitalization is 3–4 days, although it may be longer in children with bronchiolitis due to rhinovirus. The respiratory status typically improves over 2–5 days. However, wheezing persists in some infants for a week or longer.

The course may be prolonged in infants younger than 6 months (particularly those younger than 12 weeks) and those with comorbid conditions; these children often are severely affected and may require assisted ventilation.

Outcome

Bronchiolitis is a self-limited illness and resolves without complications in most previously healthy infants. However, severely affected infants, especially those born prematurely and those with underlying cardiopulmonary disease or immunodeficiency, are at increased risk for complications (e.g., apnea, respiratory failure, secondary bacterial infection).

Mortality

The overall mortality rate in children hospitalized with RSV bronchiolitis in developed countries is less than 2%. Mortality is increased in young infants (6–12 weeks) those with low birth weight and those with underlying medical conditions (e.g., underlying cardiopulmonary disease, immune deficiency).

Long-term Sequelae

Possible association with asthma: Infants hospitalized for LRTI, especially RSV, are at increased risk for recurrent wheezing and reduced pulmonary function, particularly during the first decade of life. In a prospective cohort, LRTI with RSV increased the risk for subsequent frequent and infrequent wheezing and was associated with reduced forced expiratory volume in children up to 11 years of age. However, this association was lost by the age of 13 years, perhaps due to inadequate sample size. In some studies, a correlation exists between infection with RSV and the later development of reversible airways disease. However, this may reflect the multifactorial nature of risk for asthma including a genetic predisposition to airway reactivity, exposure to environmental pollutants such as smoke, immunologic mechanisms, and

disruption of the growth and development of the lungs due to viral infection in early childhood.

IN A NUTSHELL

1. Bronchiolitis is a clinical syndrome in children less than 2 years of age characterized by upper respiratory symptoms followed tachypnea and/or wheezing.
2. Bronchiolitis is primarily caused by respiratory syncytial virus.
3. Risk factors for severe disease and/or complications include gestational age less than 37 weeks, age less than 12 weeks, chronic pulmonary disease, congenital and anatomic defects of the airways, congenital heart disease, immunodeficiency and neurologic disease.
4. Bronchiolitis is diagnosed clinically. Chest radiographs and laboratory tests are not routinely indicated.
5. Anticipatory guidance, adequate clinical monitoring and supportive management are essential. Bronchodilators may have a role in some patients.

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Chapter 39.17

Alpha-1 Antitrypsin Deficiency

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Laurell and Eriksson first described alpha-1 antitrypsin (AAT) deficiency in 1963. AAT deficiency is relatively less common condition worldwide. This genetic disease results in emphysema and chronic obstructive pulmonary disease (COPD), usually in adults but not in children. In children, AAT deficiency is an important cause for cholestasis. Liver disease including cirrhosis and hepatocellular carcinoma (HCC) may occur both in children and adults. Pediatricians are usually involved in genetic testing of the disease.

EPIDEMIOLOGY

Alpha-1 antitrypsin deficiency is the most common genetic cause of neonatal cholestasis. PiZZ is the most common phenotype in patients with emphysema secondary to AAT deficiency. AAT deficiency is usually under-recognized and mean interval between first symptom and diagnosis of AAT deficiency is reported to be 7.2 years. It is estimated that disease is diagnosed in only 5–10% of affected individuals. It is considered to be rare in India and other Southeast Asian countries.

PATHOGENESIS

Alpha-1 antitrypsin deficiency is co-dominantly inherited condition having more than 100 alleles. Expression of both alleles determines the serum levels of AAT and resulting disease severity. AAT deficiency is classified through protease inhibitor (Pi) system based on banding pattern on isoelectric focusing gel electrophoresis (F-Fast, M-Medium, S-Slow and Z-very slow), e.g., Pi ZZ, Pi SM, Pi MM, etc. Serum level of AAT less than 11 $\mu\text{m/L}$ is a risk factor for development of emphysema. The gene, *SERPINA1*, that encodes AAT is situated on chromosome.14q31-32.3. The most common Z allele is characterized by substitution of lysine for glutamic acid at position 342.

Alpha-1 antitrypsin is primarily produced within hepatocytes and reaches lungs via circulation. It is also produced locally in lungs by bronchial epithelial cells, alveolar macrophages, neutrophils and type II pneumocytes. AAT belongs to serine proteinase inhibitor (SERPIN) family and suppresses activity of trypsin, collagenase, neutrophil elastase and macrophage cathepsin enzymes. In AAT deficiency, liver disease is caused by toxic gain of function and lung disease is caused by loss of function of the protein. AAT deficiency causes polymerization of AAT in hepatocytes resulting in aggregation of misfolded protein that causes liver pathology. The disease causes imbalance between protease and antiprotease leading to enzymatic breakdown of lung tissue that results in emphysema. Mechanical damage and inflammation fueled by enhanced chemotaxis also contributes in development of emphysema. The decreased protease inhibitions

in AAT deficiency have some advantages against infections, but it may enhance ovulation, twinning, fertility and sperm migration. The environment, especially smoking, and genetic components also mediate development of emphysema in AAT deficiency.

CLINICAL FEATURES

Although, AAT deficiency has been detected during neonatal screening programs, it rarely presents with respiratory symptoms in children. AAT deficiency usually causes liver disease in children ranging from neonatal cholestasis to liver failure requiring transplantation.

In adults, AAT deficiency may cause emphysema, bronchiectasis and a spectrum of liver disease including chronic hepatitis, cirrhosis and hepatoma. Mean age of presentation of emphysema secondary to AAT deficiency is 32–41 years. Symptoms mimic COPD and asthma. Characteristic pulmonary features of AAT deficiency include early onset (as compared to COPD), emphysematous changes more in lung bases and panacinar pathology. Liver disease manifestation in children ranges from transaminitis to cirrhosis and liver failure. About 25% children having liver disease die in first decade of life and 50% develop cirrhosis. It is recommended to test for AAT deficiency in all neonates and children having unexplained liver disease.

In adults, AAT deficiency is also found to have associations with necrotizing panniculitis, vasculitis (especially c-ANCA positive vasculitis such as Wegener's granulomatosis), celiac disease, glomerulonephritis, various malignancies and pancreatitis.

DIAGNOSIS

Estimation of serum level of AAT is primary step to diagnose AAT deficiency. If AAT levels are low, isoelectric focusing (phenotyping) should be performed to conform the diagnosis and to identify AAT variants. Recently, genotyping by polymerase chain reaction (PCR) is considered diagnostic test of choice. Testing of asymptomatic children for AAT deficiency has psychological connotations and should be done along with counseling.

MANAGEMENT

Treatment of COPD due to AAT deficiency includes supportive therapy (bronchodilators, oxygen supplementation if needed, smoking cessation, antimicrobials for secondary infection) along with enzyme replacement (intravenous augmentation) therapy. Augmentation therapy consists of infusion of purified pooled human plasma AAT in a sufficient amount to raise AAT levels above threshold value. The usual dose for purified AAT is 60 mg/kg once weekly. Studies and meta-analysis regarding efficacy of augmentation therapy for AAT deficiency have inconclusive results. It is suggested that augmentation therapy may be effective for moderate obstruction as compared to mild and severe obstruction. Therapy is usually well tolerated. There is no specific therapy for liver disease due to AAT deficiency and treatment includes supportive treatment for cholestasis. Liver transplantation may be curative for end-stage liver disease.

OUTCOME

In children with AAT deficiency, liver disease is responsible for morbidity and mortality. AAT deficiency causes gradual decline in lung function in affected adults. Risk factors for rapid decline in forced expiratory volume in 1s (FEV₁) include smoking, moderate to severe obstruction, male sex, bronchodilator responsiveness and decreased serum level of AAT. In adults, respiratory failure is

BOX 3 Discharge criteria for bronchiolitis

- Patient is stable without for bronchiolitis supplemental oxygen for at least 10–12 hours prior to discharge
- Patient has adequate oral intake to prevent dehydration
- The resources at home are adequate to support the use of any necessary home therapies (e.g., inhalation therapy if the trial was successful and this therapy is to be continued)
- Education of the family is complete.

most common cause of death in AAT deficiency followed by liver cirrhosis. Risk factors for death include lower FEV₁, lower education, old age and not getting intravenous augmentation therapy.

IN A NUTSHELL

1. Alpha-1 antitrypsin (AAT) deficiency is not uncommon but an under-recognized entity.
2. In children, it usually manifests as liver disease and respiratory symptoms are rare.
3. AAT deficiency is an important cause for early onset emphysema in adults.
4. Most common Z allele produces low level of AAT that is risk factor for development of disease.
5. Augmentation therapy (intravenous infusion of purified AAT) may slow down decline in lung function and progression of emphysema.

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Chapter 39.18

Aspiration Syndromes

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Aspiration refers to the passage of foreign material into the lower airways. Small amounts of secretions from the nasopharyngeal area are commonly aspirated into the lower airways in healthy subjects, and do not lead to any problems clinically. In infants and children, small amounts of saliva and mucus are normally aspirated mostly when asleep. They are cleared quickly by the mucociliary function of the airways, and therefore do not usually cause problems. However, if the amount that enters the airways is significant enough to overwhelm these protective mechanisms, or if the material is particularly irritant, aspiration into the airways can result in lung disease in children.

Aspiration material into the airways can include foreign bodies, meconium, hydrocarbons and large amounts of water from near drowning. However, aspiration syndromes are usually referred to conditions where there is aspiration of gastric contents, oropharyngeal secretions, or food, and will be the focus of this chapter. Aspiration syndromes can manifest with a variety of clinical presentations, and depends on the type of material and amount, whether acute or chronic.

EPIDEMIOLOGY

The prevalence of gastroesophageal regurgitation among infants at 1–6 months of age in India was found to be 55%, dropping to 15% at 7–12 months and subsequently 10% at 12–24 months. However, little is reported about the prevalence of aspiration syndrome resulting from gastroesophageal reflux disease (GERD) or swallowing dysfunction in India. Chronic microaspiration is commonly underdiagnosed globally, with symptoms often attributed to other diseases of the lungs, and management is frequently suboptimal as a result.

ETIOLOGY

Broadly, aspiration syndromes results from a failure of airway protective mechanisms in preventing foreign material from entering the airways, and comprise two major types: (1) acute large volume (macro-) aspiration, and (2) recurrent small volume (micro-) aspiration. Gastric contents can be aspirated in large volumes, and may happen in children with impaired consciousness. Recurrent aspiration is predisposed by various conditions that either (1) interfere with the normal mechanisms of swallowing or (2) because of the presence of GER.

Swallowing Dysfunction

Conditions which interfere with swallowing are listed in **Table 1**. Infants who are tachypneic have dyscoordinated swallowing in relation to sucking and breathing. Acute illness can exacerbate the swallowing dysfunction in any condition, as it can lead to fatigue more quickly. Children with neurological impairment are also at risk of recurrent aspiration of saliva due to blunted cough reflex, dysfunctional swallowing, and depressed laryngeal sensation. They may not have immediate symptoms of aspiration (i.e., silent aspiration), and often present with symptoms of the lung disease as a consequence.

Table 1 Conditions associated with recurrent aspiration

Anatomical defects
<ul style="list-style-type: none"> • Macroglossia • Cleft palate • Laryngeal clefts • Tracheoesophageal fistula (particularly H-type) • Vascular rings • Achalasia cardia • Cricopharyngeal achalasia • Foreign body in esophagus
Neurological problems
<ul style="list-style-type: none"> • Decreased consciousness • Encephalopathy • Prematurity • Cerebral palsy • Hydrocephalus • Vocal cord paralysis
Neuromuscular disorders
<ul style="list-style-type: none"> • Muscular dystrophy • Spinal muscular atrophy • Myasthenia gravis • Guillain-Barré syndrome
Miscellaneous
<ul style="list-style-type: none"> • Tracheostomy • Endotracheal tube • Babies and young children who are fed with inappropriate techniques or foods

Gastroesophageal Reflux

Gastroesophageal reflux is the movement of stomach contents back up into the esophagus and sometimes into the oropharynx. It is common in young infants due to the immature gastroesophageal junction and their flat posture. In this situation, the GER usually resolves over the next year or two. When GER is associated with clinical effects, it is known as *GERD*. GERD is also commonly present in children with chronic diseases of the respiratory tract. However, the causal relationship between GERD and chronic respiratory disease is often difficult to ascertain. GERD can cause chronic respiratory diseases (by vagally-mediated reflex bronchospasm after esophageal acidification and recurrent microaspiration) and conversely, chronic respiratory diseases can predispose to GER due to:

- Hyperinflation in chronic lung diseases causing diaphragmatic flattening and thereby decreasing the efficacy of lower esophageal sphincter (LES);
- Higher negative pleural pressures in respiratory diseases increasing the incidence of GER; and
- The use of certain smooth muscle relaxants like salbutamol relaxing the LES.

PATHOGENESIS

Large volume aspiration results in hypoxemia over a rapid time-scale. Aspiration of material into the trachea leads to bronchospasm, coughing and mucus production. In infants, material reaching the top of the larynx can cause laryngospasm, while younger neonates and premature babies can experience reflex central apnea and bradycardia as a result of laryngeal receptor stimulation. Large volume aspirations could also block large airways leading to lobar/segmental collapse of distal lung. Sometimes the whole lung is collapsed.

Recurrent aspiration results in repeated damage to airways and lung parenchyma. GER brings up acid which when aspirated is toxic to the respiratory tract and causes desquamation of mucosa, damage to alveolar lining cells and capillaries, and neutrophilic inflammation. In contrast, repeated aspiration of partially digested vegetable matter and saliva with neutral pH—as seen in conditions of swallowing dysfunction—produces a foreign body reaction involving cell-mediated immunity. This results in nodular granulomas, giant cells and bronchiolitis with alveolar organization.

In some children, these pathological processes may break down local defenses against bacteria and lead to secondary bacterial infection of the lungs from organisms originating from the sinuses, nasopharynx and gastric region.

CLINICAL FEATURES

Acute large volume aspiration, especially in the context of foreign material lodged in a main airway, results in acute airway obstruction and hypoxic emergency. Other children will have lobar or segmental lung collapse, which will also give rise to hypoxia and respiratory distress due to ventilation-perfusion mismatch. In a child with GERD, there may be symptoms which suggest its presence, such as abnormal posturing and back-arching in infants (Sandifer's syndrome), abdominal pain, or vomiting with feeds. In infants, apnea may occur, and is either obstructive or due to reflex central apnea. Bradycardia may be present with apnea. Other symptoms suggestive of an aspiration event include coughing or choking soon after a feed. Coughing in a child with recurrent aspiration may occur more at night due to reflux when the child is lying flat.

Recurrent aspiration of food, gastric contents or saliva into the lower airways results in chronic pulmonary aspiration syndrome (CPA) and causes chronic or recurrent respiratory symptoms. These include chronic cough, wheeze, recurrent pneumonia, failure to thrive, and choking on feeds or secretions. CPA can occur coincidentally with other stressors like an upper respiratory infection. It can be difficult to distinguish between recurrent aspiration and other chronic respiratory diseases such as bronchopulmonary dysplasia. This is because a lot of the symptoms are similar—recurrent cough, wheeze, atelectasis and recurrent chest infections. Unless picked up and managed early enough, recurrent aspiration can lead to permanent lung injury and bronchiectasis. Clinical examination of patients with aspiration may reveal fine crackles or wheeze.

DIFFERENTIAL DIAGNOSES

Differential diagnoses of chronic recurrent aspiration can include respiratory conditions that result in chronic cough. These include bronchopulmonary dysplasia, tracheobronchomalacia, primary ciliary dyskinesia, bronchiectasis, cystic fibrosis, foreign body in the airways, and childhood interstitial lung disease.

APPROACH TO DIAGNOSIS

Children with aspiration syndromes often have multisystemic problems, and the evaluation of a child suspected of aspirating should involve a multidisciplinary team. A careful history should be obtained with regards to the presence of GERD. It is worth observing how the child feeds, paying attention to how the child sucks and swallows, and if there is any cough, vomiting, or choking. Drooling or excess saliva pooling in the mouth may suggest a problem with swallowing. Examination may reveal signs of airways or lung aspiration on auscultation, particularly after feeding.

Investigations for the Presence of Gastroesophageal Reflux

A *contrast swallow* is helpful to look for structural abnormalities that may result in narrowing of the esophagus (e.g., vascular rings), hiatus hernia, or tracheoesophageal fistula (particularly H-type fistulae which often require a proper prone esophagram to diagnose). The study allows the assessment of food transport down the esophagus. Extending this to a barium meal allows the investigation for the presence of GER (although limited by the short duration of the study), and also the speed of gastric emptying.

Gastroesophageal scintigraphy (milk scans) involves ingestion of a radiolabeled milk with serial images recorded. This study may be used to diagnose and quantitate reflux, but late images (24 hours) showing isotope in the lungs indicates pulmonary aspiration. The sensitivity of this procedure is very low and hence a normal study does not rule out aspiration.

24-hour esophageal pH monitoring (pH study) has been considered the gold standard for diagnosing GERD, but its limitations are being increasingly recognized. Nonacid reflux, which is equally important, is undetectable by pH monitoring. Also, traditionally, gastroenterologists interpret pH results based on the proportion of time that esophageal pH is less than 4. However, even a single bad reflux can give rise to pulmonary aspiration. For these reasons, pH monitoring is yet to be validated for extraesophageal manifestations of GER.

Multichannel intraluminal impedance study can be used to detect acid and nonacid reflux using a probe that detects change in electrical resistance during the passage of food between electrodes at different levels along the pharynx and esophagus. The study can distinguish between air, liquid and solid reflux, and their direction of flow. As the level of reflux can be measured, the number of high level reflux episodes which are more likely to penetrate into the airways can be defined. Its use is currently limited by its availability in only a limited number of centers, and a lack of evidence on how the study results should be interpreted to diagnose GER in children.

An *esophagoscopy* can be done to evaluate for esophagitis secondary to GER.

Investigations for Aspiration

Investigations for small volume aspiration are generally low on sensitivity and specificity. To assess swallowing, a clinical evaluation by a qualified speech and language therapist can be initially carried out. This can provide information on feeding behaviors of the child, and is a good screening exercise for the possibility of aspiration.

A *video fluoroscopic swallow study* (VFSS) has the ability to evaluate the oral pharyngeal and esophageal phases of swallowing directly. It will help detect aspiration of contrast material into the trachea. Different food textures and amounts can be investigated at various stages of swallowing. Owing to the episodic nature of aspiration, a normal VSS cannot entirely rule out aspiration of feeds.

Fiberoptic endoscopic evaluation of swallowing (FEES) allows the direct visualization of swallowing, and has the benefit of no sedation or radiation exposure, although more invasive than the other tests described earlier. A fiberoptic scope is passed through the nose and placed between the soft palate and epiglottis. The larynx is observed while the patient is fed with various types of foods (varying in consistency, including consistencies of the child's usual foods). Swallows are visualized directly by the physician and the child's home caregivers *via* a video monitor. The ability of the caregiver to observe the aspiration event as well as the effectiveness of feeding techniques directly provides strong feedback and reinforcement. FEES can also be used to assess for salivary aspiration which can also be visualized directly.

If salivary aspiration is suspected, *radionuclide salivagrams* can be used whereby tracer activity in the trachea following application in the buccal space indicates aspiration of saliva.

The suctioning of dye-stained secretions in patients with a tracheostomy who have been given dye on the tongue or mixed into feeds has also been used as a test for CPA in tracheotomized children.

Bronchoscopy can identify structural defects such as a laryngeal cleft and H-type tracheoesophageal fistula and can also reveal inflamed mucosa around the larynx indicating acid contact. The large airways may appear inflamed. A lipid-laden macrophage index (LLMI) based on the number of lipid-filled macrophages in bronchoalveolar lavage (BAL) has been used as a marker of inflammation but not favored due to false-positive results, lack of reproducibility and high interobserver variability.

Chronic aspiration typically presents radiographically as hyperaeration, subsegmental or segmental infiltrates and peribronchial thickening (**Fig. 1**). Bronchiectasis may also eventually be seen. The dependent areas of the lower lobes as well as posterior upper lobe segments are usually involved. Chest X-rays are not sufficiently sensitive to detect subtle changes, and a normal X-ray does not rule out aspiration.

A *computed tomography* (CT) scan of the chest is not usually necessary, but in long-standing or severe cases with chronic aspiration, nonspecific findings like tree-in-bud opacities and bronchiectasis may be seen (**Fig. 2**).

MANAGEMENT

Managing an Acute Event

For an acute aspiration event that is witnessed, immediate therapy should be instituted. These include turning the patient's head to the side, suctioning of the airway, and giving oxygen if the patient's SpO₂ is low. Antibiotics in anticipation of a secondary bacterial infection is not always necessary but may be indicated if the child is at risk of significant deterioration due to poor premorbid state (e.g., with pre-existing severe respiratory disease). Fever, mucopurulent secretions, raised inflammatory markers and leukocytosis are clues to an evolving bacterial infection.

Treatment of aspiration syndromes depends on the cause. If there is a structural problem, this will need to be repaired if possible.

Treating Gastroesophageal Reflux Disease

Medical and conservative therapies are initially chosen for children with GERD. Feeding in a more upright position can be performed, particularly in infants. Feed thickeners or reducing the volume of each feed may help in mild cases. In the older child, foods that exacerbate symptoms of GER should be avoided (e.g., caffeine and spicy foods). If the child is overweight, a weight loss program should be carried out. Acid suppression with H₂ receptor antagonists (ranitidine 2–4 mg/kg BD) or proton pump inhibitors (PPIs [proton-pump inhibitors], e.g., omeprazole 0.7–3 mg/kg OD) will reduce acid reflux. Although the efficacy of PPIs is proven for reflux esophagitis, their efficacy is not established for CPA. Prokinetic drugs to increase gastric emptying such as domperidone (0.25 mg/kg TDS) can also be tried.

Jejunal feeding by way of a nasojejunal tube (NJ tube) is sometimes used either as a bridge to surgery or in children who are not candidates for surgical treatment. NJ feeding allows adequate feeding and may reduce respiratory infections but do not guarantee elimination of GERD and therefore significant aspiration can still occur. Jejunal feeding has to be continuous (no bolus feeding) and risks intestinal obstruction, intussusception, jejunal perforation, and tube displacement.



Figure 1 Bilateral infiltrates on a chest radiograph with subsegmental atelectasis in the upper zones of a supine infant with recurrent aspiration of oropharyngeal secretions

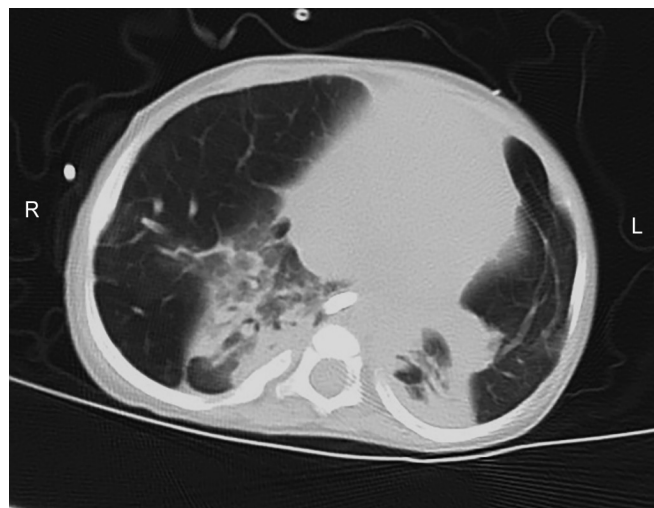


Figure 2 Computed tomography (CT) scan of the chest of a 2-year-old child with a 1-year history of recurrent oropharyngeal and gastric aspiration. There is partial collapse and consolidation of both lower lobes with patchy atelectasis on the right side

Surgery

Surgical options such as fundoplication should be considered if medical therapy is not effective and GERD is present. It can successfully resolve reflux, and subsequent respiratory symptoms of aspiration, in most children. The operation is however less successful in neurologically impaired children, with higher failure rates in this group of patients. If there is esophageal dysmotility, fundoplication may also increase the risk of dysphagia, and impede flow of food and saliva through a tight gastroesophageal junction, worsening aspiration.

Managing Swallowing Dysfunction

In swallowing dysfunction, feeding should be limited to foods with consistencies that are well tolerated, and to an amount and rate that does not result in aspiration (e.g., small frequent feeding). Nasogastric or gastrostomy feeding may be used, as long as there

is not significant GER. Percutaneous button gastrostomy has made this a useful method for those with severe swallowing dysfunction.

If there is a problem with aspiration of saliva, e.g., in children with swallowing dysfunction, several measures can be performed. The child can be nursed with the head positioned such that the secretions can drain out from the mouth (this can be aided with gentle suctioning). Medications to reduce the volume of saliva can be used, e.g., hyoscine, scopolamine (1.5 mg skin patch), and glycopyrrolate (0.04–0.1 mg/kg/dose, 3–4 times a day). However, there is a risk that the thickening of secretions as a result of these medications makes suctioning more difficult, with increased risk of mucus plugging and atelectasis. Anticholinergic side effects such as decreased bowel movements and urinary retention can also occur. Injection of the salivary glands with botulism toxin can reduce the amount of saliva produced; this is guided by ultrasound. The effect of this procedure is short-lasting and repeat injections would have to be given in future.

Surgery

Posterior migration or ligation of the salivary ducts and surgical removal of salivary glands are surgical options to reduce the amount of salivary secretion. Placement of a tracheostomy tube may be required, if other medical or surgical therapies fail, mainly for airway toileting. If aspiration from oral secretions is life-threatening over a prolonged period and unresponsive to the earlier measures, laryngotracheal separation procedures with tracheostomy have been performed in some centers to reduce aspiration into the airways.

Key aspects of treatment are summarized in **Box 1**.

BOX 1 Treatment of aspiration syndromes

- Acute aspiration events should be treated immediately
- Antibiotics are started, if the child already has poor reserves, or when signs of secondary bacterial infection develop
- If the cause is a structural defect, the defect will need to be repaired
- If GER is present in infants, correct positioning, smaller, more frequent feeds, and feed thickeners can help
- Lifestyle modifications such as avoidance of certain foods and weight management can improve GER, if indicated
- Further treatments of GER include medications for acid suppression, prokinetics, jejunal feeding, or fundoplication
- Swallow dysfunction can be managed by limiting foods to those with consistencies that are well tolerated, or with nasogastric/gastrostomy feeding
- Aspiration of oral secretions can be managed with head positioning, suctioning, medications to reduce the volume of secretions, botulism toxin injection of salivary glands, ligation of salivary ducts, or laryngeal closure surgery with tracheostomy.

PROGNOSIS

Most patients will recover within a few weeks, if an aspiration event is adequately treated and managed without complications such as pneumonia. If recurrent aspiration is left untreated, it may lead

to complications such as recurrent pneumonitis, lung damage, bronchiectasis, bronchiolitis obliterans and failure to thrive.

Sometimes, children with clinical evidence of recurrent aspiration will have negative test results for swallowing dysfunction or GERD. A trial of no feeding by mouth and NG feeding could improve their respiratory symptoms. These cases highlight the difficulties in establishing the diagnosis of CPA and the importance of clinical judgment in suspected cases.

PREVENTION

Aspiration syndromes are often underdiagnosed, and early recognition of clues pertaining to an aspiration syndrome is important to reduce the risk of significant airway disease. Prevention of further aspiration is the goal of treatment once an aspiration syndrome is recognized, by having a logical approach to work-up and treatment.

IN A NUTSHELL

1. Aspiration is the penetration of foreign material into the airways and subsequently the lungs.
2. Aspiration syndromes usually result in recurrent aspiration of gastric contents, oropharyngeal secretions or food overtime, and can lead to significant lung disease.
3. Aspiration syndromes are underdiagnosed, and often detected only late in the disease course when permanent lung changes have occurred.
4. Children at risk for recurrent aspiration are usually those with anatomical and neurological defects that interfere with the normal process of swallowing, or with significant GER.
5. The evaluation of a child suspected of aspiration should involve a multidisciplinary team.
6. Work-up should be targeted at finding out the underlying cause for aspiration, and the extent of airways and lung injury as a result of aspiration.
7. The treatment goal is to address the causes of aspiration to prevent future aspiration events from occurring.

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Chapter 39.19

Preschool Wheeze and Bronchial Asthma

KR Bharath Kumar Reddy, Samatha Sonnappa

PRESCHOOL WHEEZING

Wheeze is an audible manifestation of airway oscillations caused by airflow limitation, irrespective of the underlying cause. Wheezing in the preschool years is extremely common and it is estimated that approximately one in three children will have at least one episode of wheeze prior to their third birthday, and by 6 years of age, this figure increases to almost 50%. This is likely due to the pathophysiologic properties that predispose infantile lungs to wheeze. Infants' bronchioles (compared to older children and adults) have decreased smooth muscle content, hyperplasia of mucus glands and a smaller radius, which, in turn, increases resistance considerably. These factors increase the risk of obstruction and may manifest as cough, wheeze, chest tightness, shortness of breath, or tachypnea. Wheezing in the preschool years is heterogeneous and the long-term prognosis varies from complete recovery to persistent asthma. This section will focus on preschool children with recurrent wheeze. Recurrent wheezing is defined as more than three episodes of wheezing in the past year that lasted more than a day and affected sleep.

EPIDEMIOLOGY

The most common cause of wheezing, whether primary or recurrent, during the first few years of life is infection with respiratory viruses, most commonly respiratory syncytial virus and human rhinovirus. All children are infected with respiratory viruses during early childhood and nearly one-half wheeze during at least one of these infections. A number of risk factors for wheezing with respiratory viruses during early childhood have been identified by birth-cohort studies. Maternal smoking, male sex, older siblings and daycare attendance during infancy increase the risk for early childhood wheezing illnesses.

ETIOLOGY

Preschool wheeze is a syndrome and not a single entity. Within the syndrome of preschool wheeze, several phenotypes have been proposed, as shown in **Box 1**. These phenotypes are used to study risk factors, prognosis and response to treatment. However, these phenotypes probably represent different facades of the same entity, as there is significant overlap between the phenotypic categories.

PATHOPHYSIOLOGY

Pathological studies have been relevant in determining early structural changes as well as guiding treatment. From the few studies that used bronchial biopsies or bronchoalveolar lavage, it is clear that the inflammatory reactions in preschool children with wheeze differ from those in older children with established asthma. Two cross-sectional studies have suggested that in preschool wheezers, there may be a window of around 18 months between symptom onset and development of airway wall changes consistent with asthma. In the first study, infants (median age 12 months) were investigated for severe respiratory symptoms, using infant lung function, bronchodilator reversibility and rigid bronchoscopy. Despite severity of symptoms, there was no evidence of airway

BOX 1 Preschool wheeze phenotypes

Phenotype based on time course:

- *Transient wheeze:* Wheeze during the first 3 years of life and stops by age 6 years
- *Persistent wheeze:* Wheeze in the first 3 years of life and continue to wheeze at age 6 years
- *Late-onset wheeze:* No wheeze in the first 3 years of life but wheeze at age 6 years

Phenotype based on symptom-pattern:

- *Episodic (viral) wheeze:* Wheeze at discrete times, often with evidence of viral colds and characterized by no symptoms between episodes
- *Multiple-trigger wheeze:* Wheeze with discrete exacerbations and symptoms between episodes

Phenotype based on atopic status:

- *Atopic wheeze:* Various defined as those with elevated IgE and/or allergic sensitization to allergens with or without eczema. Symptomatic at any age but most before age 6 years
- *Nonatopic wheeze:* Children wheeze with viral infections during the first 3 years of life and may continue to do so or stop at school-age.

inflammation or reticular basement membrane thickening, even in infants with documented atopy and bronchodilator reversibility. In the second cross-sectional study, infants (median age 30 months) with confirmed severe wheezing episodes showed evidence of eosinophilic inflammation and reticular basement membrane thickening albeit less marked than in children with severe asthma. Other studies have confirmed that eosinophilic inflammation is not prominent in episodic (viral) wheeze.

Epidemiological evidence has shown that transient wheezers (who may have an episodic [viral] or multiple-trigger phenotype, but are probably more likely to have the former) are born with airflow obstruction, whereas those with persistent wheeze (which again may be episodic [viral] or multiple-trigger phenotype, more likely the latter) have normal lung function soon after birth that becomes abnormal by age 4–6 years. Thus, attention focuses on the antenatal period for the transient wheezers and the immediate postnatal years for the persistent wheezers, the likely future asthmatics in mid-childhood. Risk factors for persistence of wheeze into adulthood include female sex, atopy, airway hyper-responsiveness, poor lung function in childhood and smoking.

CLINICAL PRESENTATION

The typical symptoms include expiratory wheezing and cough. Shortness of breath and dyspnea are the other characteristic symptoms. The physical examination in the preschool child with wheeze may be normal at consultation as intermittent symptoms are most common at this age. If symptomatic at the time of examination, physical findings commonly include polyphonic expiratory wheeze as a manifestation of diffusely narrowed small airways. Coarse crackles may be heard from mucus in the large airways. During an acute exacerbation, labored breathing with intercostal, suprasternal and substernal retractions may be present, along with an audible wheeze. In the preschool child who is asymptomatic on examination, the diagnosis is dependent on a careful history of previous symptoms.

APPROACH TO DIAGNOSIS

Initial evaluation of a child with recurrent wheeze depends on the likely etiology. A thorough history in a wheezy child that includes details of the wheezing episode, such as onset, duration and associated factors often provides clues to allow prioritization of diagnostic possibilities listed in **Table 1**. In a child with a clear history of episodic (viral) or multiple-trigger wheeze, no initial

investigations are necessary. A chest X-ray is not generally required, but may be helpful if other diagnoses need to be considered. A trial of bronchodilator through a spacer may be diagnostic and therapeutic in a child who is seen while symptomatic. Pulmonary function testing, a valuable tool in aiding asthma diagnosis is not frequently used in preschoolers, but can be successfully performed in children as young as 3 years.

Further evaluation with investigations as listed in **Table 1** can be considered in a step-wise manner in wheezers with a more complex history and in those not responsive to a trial of inhaled corticosteroids.

Differential Diagnoses

The younger the child at presentation, the broader the differential diagnosis, emphasizing the importance of a higher index of suspicion for other causes of wheezing in the preschool child, as listed in **Table 1**.

MANAGEMENT

Apart from the environmental control, allergen avoidance and parent education, pharmacological treatment should be focused on symptom prevention and improving the long-term outcome of preschool wheezers. Acute symptoms are treated with short-acting beta-agonists, systemic corticosteroids and oxygen in severe cases. Oral steroids are not indicated in preschool children with attacks of wheeze who are well enough to remain at home and in many such children, especially those with episodic viral wheeze, who are admitted to hospital.

Preventive Therapy

The use of inhaled or oral corticosteroids in preschool wheezers is common in clinical pediatric practice. Most children with preschool wheezing will outgrow their symptoms and do not need any preventive treatment especially when the symptoms are mild

and infrequent. However, when symptoms are severe or frequent, initiating preventive treatment will reduce symptoms and improve quality of life. Treatment options include intermittent montelukast for episodic (viral) wheezers and prophylactic low-dose inhaled corticosteroids with bronchodilators (as per need) and montelukast for multiple-trigger wheeze. Regular, careful re-evaluation of children's symptoms is essential as the wheeze phenotype can change over time in preschool children. An approach to treatment is given in **Table 2**.

PROGNOSIS

Parents frequently want to know whether their child will continue to have symptoms and require drug treatment into school age and beyond. Several randomized controlled trials show that early use of inhaled corticosteroids, whether continuously or intermittently with viral colds, does not affect progression of disease and treatment should be solely focused on control of current symptoms.

The asthma predictive index (API) is a commonly used clinical tool that allows for identification of children at maximum risk for persistent wheeze at school age (**Table 3**). To have a positive API, a child must wheeze before age 3 years and have either one of two major criteria or two of three minor criteria. Children with recurrent wheeze before age 3 years and a positive API at age 3 years were nearly 10 times more likely to have active asthma at age 6 years and nearly 6 times more likely to have asthma at age 13 years than children with a negative API. Even children with only one wheezing episode before age 3 years were 2.6–5.5 times more likely to have persistent symptoms at ages 6 years and 13 years, respectively, if their APIs were positive. Thus, this index can be used to guide caregivers and clinicians as to the likely course of a child's subsequent wheezing.

However, it should be noted that API and other clinical predictive indices for future risk of asthma while useful in group

Table 1 Differential diagnosis of recurrent wheezing in preschool children and suggested investigations

Diagnosis	Main clinical features	Evaluation
Episodic (viral) wheeze	Triggered only by viral infections (colds)	Good history and examination
Multiple-trigger wheeze	Triggered by colds and other factors such as allergy, exercise	Good history and examination
Aspiration syndromes	Chronic cough, vomiting or poor weight gain	pH study and contrast studies to assess swallowing disorders and gastroesophageal reflux
Inhaled foreign body	Chronic cough usually with a history of prior episode of acute coughing or choking	Chest X-ray, bronchoscopy
Airway malacia	Stridor and wheeze poorly responding to bronchodilators and inhaled steroids	Flexible bronchoscopy
Congenital anomalies (vascular ring)	Stridor and wheeze poorly responding to bronchodilators and inhaled steroids	Contrast studies, echocardiogram, CT chest
Bronchiectasis	Recurrent cough and wheeze frequently but not always associated with gastrointestinal symptoms and poor weight gain Chronic rhinosinusitis and/or otitis media	Bronchiectasis work-up to rule out immunodeficiency, primary ciliary dyskinesia, cystic fibrosis

Abbreviation: CT, computed tomography.

Table 2 Approach to treatment in preschool children with recurrent wheeze

Step 1: Trial of inhaled corticosteroids or montelukast in standard dose for 4–8 weeks
Step 2: Stop treatment—either there has been no improvement, in which case further escalation is not valuable; or symptoms have disappeared spontaneously or as a result of treatment If there is no benefit and the symptoms are troublesome, further investigation is recommended
Step 3: Restart treatment only if symptoms recur; then reduce treatment to the lowest level that achieves symptom control

Table 3 Asthma predictive index

Major criteria	Minor criteria
<ul style="list-style-type: none"> • Parental history of asthma • Physician diagnosed atopic dermatitis 	<ul style="list-style-type: none"> • Physician diagnosed allergic rhinitis • Wheezing unrelated to colds • Peripheral eosinophilia > 4%

Note: A child with either one major or two major criteria; and presentation for 3 years of age is considered positive for API.

studies are of little use in individual patient care. They have a high negative predictive value and a poor positive predictive value (typically positive predictive values 44–54, negative 81–88).

IN A NUTSHELL

1. Several phenotypes of preschool wheezers are described based on wheeze onset and duration, symptom pattern and atopic status.
2. Individual children can change phenotypes with time.
3. It is difficult to predict which infants and preschoolers with wheeze will subsequently develop asthma.
4. Scoring systems are available but are of limited predictive value, and may not apply at individual level.
5. Inhaled corticosteroids control symptoms and exacerbations in recurrent wheezers, but are not disease modifying.

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BRONCHIAL ASTHMA

Asthma is one of the most common chronic diseases of childhood. It is defined as a chronic inflammatory disorder of the lower airways characterized by recurrent episodes of variable, reversible airflow obstruction and airway hyper-responsiveness (AHR) manifested as recurrent wheeze and cough. AHR is the inherent tendency of the bronchi to narrow in response to different stimuli, such as allergens, irritants or infections.

EPIDEMIOLOGY

The prevalence of asthma is increasing worldwide with an estimate of 1–18%. The International Study of Asthma and Allergies in Childhood estimated asthma prevalence in India to be 6.2–6.8% in the 6–7 year olds and 6.4–6.7% in 13–14 year olds, with more males affected than females.

PATHOLOGY

The pathological changes in asthmatic lungs are characterized by edema, increased mucus secretion with mucus plugging, smooth muscle contraction, infiltration with inflammatory cells, predominantly eosinophils and bronchiolar epithelial cell desquamation and denudation. These changes are acute and reversible. Chronic changes associated with airway remodeling in children include an increased vascularity of subepithelial tissue with smooth muscle hyperemia, hypertrophic smooth muscle, thickening of basement membrane, subepithelial deposition of structural proteins like type IV collagen, and loss of airway distensibility.

Airway obstruction in asthma results from a combination of bronchospasm, mucosal edema and mucus plugging. This leads to increased resistance to airflow through the larger airways and decreased flow through the smaller airways due to narrowing and early closure resulting in hyperinflation and retention of air. Due to regional differences in the resistance and uneven circulation to the alveoli, there exists a ventilation-perfusion mismatch. This leads to decreased oxygenation and hypoxemia, hyperventilation and respiratory alkalosis in early stages followed by CO₂ retention and respiratory acidosis in more severe cases.

IMMUNOPATHOGENESIS

Asthma is influenced by an interaction between genetic and environmental factors which leads to AHR with structural and functional changes in the airways. Genetically predisposed individuals are shown to react to certain *inducers* (Table 4), which generate an immune response. Common genes associated with asthma include the interleukin-4 (*IL-4*) gene on chromosome 5 (proinflammatory), *ADAM-33* (metalloproteinase family), *IL-12* on chromosome 5q31, genes for prostanoid DP receptors and polymorphisms in the beta-adrenergic receptors.

Th2 cytokine-mediated predominance is seen with a chronic activation of different cell lines which include inflammatory cells like mast cells, eosinophils, lymphocytes, macrophages and dendritic cells and structural cells like epithelial cells and smooth muscle cells. These stimulate the production of Th2 mediators, IgE, IgG4 and IgG1. *Enhancers* (Table 4) are known to aggravate this response on repeated exposure and stimulate a heightened Th2 reaction with T helper cells, mast cells and eosinophils, resulting in AHR. The role of anti-inflammatory therapy and immunotherapy is targeted at this stage of pathogenesis. *Triggers* (Table 4) are agents that stimulate symptoms in a child predisposed to wheezing due to prior sensitization with these *inducers*. As per the *Hygiene Hypothesis*, this induction can be prevented by avoidance of allergens or early exposure to endotoxins.

Allergens

There are numerous indoor and outdoor allergens of clinical significance which are shown to be associated with asthma. Allergen proteins which have a sequence homology with other proteins in the body, a molecular weight of 15–40 kD, soluble in aqueous solutions and with a tertiary structure and biologic properties foreign to the body are shown to stimulate an IgE response in children on inhalation. Indoor allergens and those with a larger size (> 5 microns in diameter) are shown to create a more intense allergic reaction (e.g., mite fecal particles and pollen).

Response to Allergens

An *early response* on subsequent exposure to a sensitized allergen is seen with an immediate hypersensitivity reaction and an IgE-mediated response associated with decline in forced expiratory volume in one second (FEV₁). A *late response* includes infiltration with eosinophils and release of eosinophil products, like major

Table 4 Factors that potentially influence pathogenesis of childhood asthma

Inducers	Enhancers	Triggers
<ul style="list-style-type: none"> Dust mite (<i>Dermatophagoides pteronyssinus</i>) Cockroach (<i>Blattella germanica</i>) Grass pollen (<i>Sorghastrum nutans</i> and <i>Parthenium hysterophorus</i> in India) Fungus (<i>Alternaria</i> and <i>Aspergillus</i>) Cat (<i>Felis domesticus</i>) Dog (<i>Canis familiaris</i>) Mouse (<i>Mus domesticus</i>) Rat (<i>Rattus norvegicus</i>) 	<ul style="list-style-type: none"> Viral infections Ozone Sulfur dioxide Particulate matter Diesel particles Endotoxins Comorbid conditions: Rhinitis, sinusitis and gastroesophageal reflux 	<ul style="list-style-type: none"> Exercise Cold and dry air Environmental tobacco smoke Pollution Histamine/methacholine Strong and noxious odors or fumes of perfumes and cleansing agents Crying, laughter or hyperventilation

basic protein and eosinophils cationic protein, which are toxic to the epithelium. Mast cells are activated, which release histamine, cysteinyl leukotrienes, platelet activating factor, IL-5 and other chemokines.

Viral Infections

Viruses which have shown to have an association with asthma include rhinovirus, respiratory syncytial virus, influenza, parainfluenza, adenovirus and human metapneumovirus. Possible hypotheses of how these viruses could induce asthma include the virus stimulating an exaggerated allergic response in an atopic individual, or the upper respiratory tract infection triggering a neurologic, cellular or cytokine-mediated effect in the lungs. Thus, the viral infection starts off a cascade of atopic events which maintains the persistent airway inflammation.

An increase in the eosinophils within the airway with release of inflammatory markers such as TGF- β and Ki67 is thought to induce changes in the extracellular matrix. Repeated bronchoconstriction generates mechanical forces contributing to tissue remodeling. This results in a decline in lung function over time and a subsequent loss of bronchodilator reversibility. Based on the immunopathogenesis of asthma, limited treatment options are available:

- Anti-inflammatory agents, such as oral and inhaled corticosteroids, leukotriene antagonists and anti-IgE monoclonal antibodies (omalizumab);
- Allergen-specific treatment, such as avoidance and immunotherapy.

CLINICAL FEATURES

Symptoms

Cough

Intermittent, chronic and a dry nature characterize the cough in asthma. Early morning worsening of cough or following physical exertion is classical. Chronic wet cough should raise the possibility of other etiological factors and needs to be investigated.

Wheeze

Expiratory wheeze noted at night or following exercise characterizes asthma. Improvement following bronchodilator use increases the possibility of asthma. Lack of improvement with bronchodilator and steroid medication requires aggressive investigation to rule out other mimickers of asthma.

Shortness of breath, chest tightness or chest pain are other symptoms in acute exacerbation.

Signs

Chest examination may be normal, with an occasional expiratory wheeze or prolonged expiratory phase elicited on deep breathing. Improvement of wheeze with inhaled short-acting beta-2 agonists within minutes is diagnostic of asthma. Accessory muscles use,

intercostal retractions and nasal flaring can be seen in severe cases with an acute exacerbation. Inflammatory obstruction of the airways can lead to right middle or lower lobe collapse. Crackles can be heard due to increased mucus and exudates in the large airways or associated segmental collapse.

DIFFERENTIAL DIAGNOSIS

All that wheezes is not asthma. Many conditions present with wheezing in early childhood, as described in previous chapters. Persistent chronic dry cough for more than 4 weeks with specific triggers and exacerbating factors can raise the suspicion of asthma. The three most common causes of night-time coughing in children include—(1) asthma, (2) gastroesophageal reflux disease (GERD), and (3) sinusitis with postnasal drip. The time of the night at which cough is predominantly present can give a clue to differentiate them. Early morning cough (between 3 am and 5 am) or just prior to waking up is classical of asthma; cough present immediately following feeding and lying down early at night is suggestive of GER and that which presents late at night following a postnasal drip suggests rhinosinusitis.

DIAGNOSIS

The diagnosis of asthma in children is predominantly made on a clinical basis. A typical symptom pattern which includes history of recurrent episodes of cough, wheeze, hurried breathing and shortness of breath which is triggered on exposure to specific stimuli is a starting point to the diagnosis of asthma. Personal history of atopy such as allergic rhinitis, eczema, allergic conjunctivitis, and food or aeroallergen sensitization should be enquired into. Family history of atopy and/or asthma increases the possibility of the diagnosis.

Chest X-ray is not routinely indicated in asthma, unless other conditions which mimic asthma need to be ruled out. Radiographs show bilateral hyperinflation and peribronchial thickening.

Pulmonary Function Tests

Pulmonary function tests (PFTs) represent an integral component of clinical management in school-aged children with asthma, and are being increasingly used in preschool children. Spirometry is the most commonly applied lung function test and can be applied in a wide variety of locations and across the ages. Spirometric indices commonly measured are forced vital capacity (FVC), FEV₁ and forced expiratory flow rate over 25–75% of FVC (FEF_{25–75}). FEV₁ less than or equal to 80% predicted for age, sex and ethnicity is suggestive of airflow obstruction. While spirometry is useful for determining the severity of asthma, monitoring and guiding treatment, *normal spirometry* does not necessarily infer normal lung function. Many intermittent or mild asthmatics have normal spirometry between acute exacerbations. Documentation of bronchodilator reversibility (BDR) of airflow obstruction following inhalation of a bronchodilator is central to the definition of asthma.

If airway obstruction is demonstrated at baseline, an inhaled bronchodilator (salbutamol 200 µg) should be administered and spirometry repeated after 15–20 minutes. An improvement of at least 12% in FEV₁ is considered as positive BDR and is consistent with a diagnosis of asthma.

In children less than 5 years of age, other techniques that require only tidal breathing for assessing lung function include impulse oscillometry or specific airway resistance.

Use of peak flow meter to measure peak expiratory flow rate (PEFR) although commonly used should not be used to diagnose or monitor asthma as it is reflective of obstruction only in the large airways.

Bronchial Provocation Tests

Airway hyper-reactivity to methacholine, histamine or hypertonic saline in a child with *normal* FEV₁ can aid in the diagnosis of asthma. A 20% fall in FEV₁ induced by a concentration of methacholine less than 4 mg/mL is considered positive. However, these tests are not routinely used in clinical practice, as airway stimulants should be carefully dosed and monitored.

Exercise Tolerance Test

An exercise test such as running on a treadmill can be useful in diagnosing asthma in children with a history suggestive of exercise induced bronchospasm. PFT should be measured at baseline and serial measurements every 5 minutes for 20 minutes postexercise. A more than or equal to 12% drop in FEV₁ or more than or equal to 25% in FEF_{25–75} is diagnostic of exercise induced asthma.

Fractional Exhaled Nitric Oxide

Fractional exhaled nitric oxide (FeNO) is a surrogate marker of eosinophilic airway inflammation and a good predictor of corticosteroid response. It aids in the assessment, management and long-term monitoring of asthma. Normative values in the Indian population are inadequate. Western data indicate values more than 20 ppb to be suggestive of airway inflammation.

TREATMENT OF ASTHMA

There are a large number of guidelines on the management of asthma; however, the key messages of most of them remain similar. The principal goal is disease control using least possible medication.

Education of Parents and Caregivers

Asthma education is a continuous and dynamic process. Education should highlight chronic nature of the disease, the recognition of asthma symptoms, different types of medication, need for long-term medication, importance of compliance and adherence and a demonstration of use of inhalers and spacers. Self-management will help maintain good control of asthma and also identify and avoid triggers. A written personalized *Asthma Action Plan* should be issued to each patient indicating the daily medication regimen along with management of asthma exacerbations.

Identification and Avoidance of Triggers

Avoidance of triggers may have a beneficial effect on disease activity. Reduction or elimination of problematic environmental exposures is the key in asthma control. Efforts need to be focused on avoiding perennial and indoor allergens which can potentially decrease asthma symptoms, medication requirements, AHR and exacerbations. This however requires avoidance of the offending agent for a sustained period of days to weeks. Avoidance and control of the exposure to environmental tobacco smoke and other fumes has shown to significantly control and reduce exacerbations

in children with asthma. Prior to advising avoidance of specific allergens, significant proof needs to be ascertained by a careful clinical history, skin prick testing and/or specific IgE measurement. Skin prick testing and/or specific IgE measurement can help, particularly if there are few identified or suspected triggers.

Treating Comorbid Conditions

The most common causes of chronic coughing in children include rhinitis, sinusitis and GER in addition to asthma. Effective management of these comorbid conditions is shown to reduce medication requirement, disease severity and asthma symptoms. Seasonal or perennial allergic rhinitis complicates asthma in nearly 90% children. Mouth breathing in patients prevents the function of humidifying, warming and filtering of irritants performed by the nose. An associated sinusitis significantly contributes to failure in response to asthma medication. Treatment of these conditions by topical therapy with nasal saline irrigation, intranasal corticosteroids and a 2–3 weeks course of antibiotics in children with sinusitis significantly improves AHR, asthma symptoms, medication use and inflammation.

Regular Assessment and Monitoring

Regular clinic visits every 2–4 weeks depending on severity of symptoms is recommended until good asthma control is achieved. Subsequently, 2–4 check-ups per year can maintain good asthma control. Spirometry is recommended annually in well-controlled patients and more frequently if required.

Pharmacotherapy

A *step-wise* management strategy for pharmacotherapy is recommended (**Figure 1**).

- Initial assessment of asthma severity if no medication has been used previously
- Choose the step at which treatment needs to be initiated
- Achieve early and rapid control
- Reassess disease control regularly
- Step-up therapy when control is not achieved in 1–3 months and step-down therapy when control is good in 3 months.

Assessment of Severity

The National Asthma Education and Prevention Program (NAEPP) expert panel report classifies asthma severity as mild intermittent, mild persistent, moderate persistent and severe persistent, based on frequency of day-time and night-time symptoms, degree of airflow obstruction on spirometry and peak flow variability. This guideline insists on controller therapy in children with the following:

- Needing reliever medication at least three times per week
- Night awakenings at least three times per month
- Refill of reliever medication three times a year
- Acute exacerbations at least three times per year and
- Short course oral steroids at least three times a year.

All persistent forms of asthma are treated with inhaled corticosteroids (ICS) either alone or with combination depending upon the severity of disease.

Reliever Medication

Relievers produce bronchodilation and immediate relief of symptoms. Short-acting bronchodilators like salbutamol act on beta-receptors in the airway producing bronchodilation and are the first line of management in children of all ages. Other drugs include levosalbutamol and terbutaline. They act immediately and the effect lasts for 4–6 hours. Due to their quick and better effect on airway smooth muscle and reduced systemic effects, inhaled

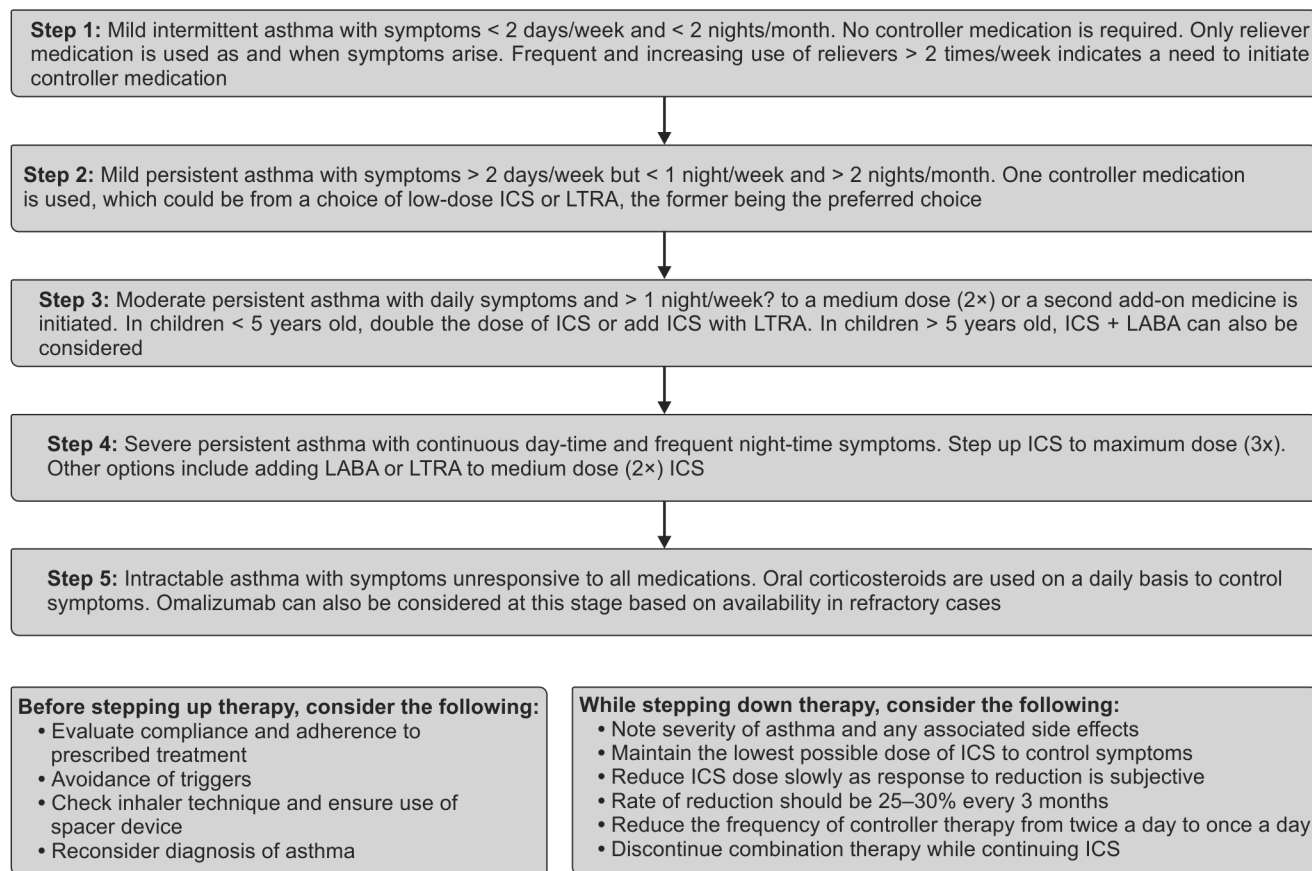


Figure 1 Step-wise approach to the management of asthma in children

Abbreviations: ICS, inhaled corticosteroids; LABA, long-acting beta-2 adrenergic agonists; LTRA, leukotriene receptor antagonists.

bronchodilators are preferred over oral bronchodilators. Side effects include tachycardia and tremors, both of which are dose dependent. Anticholinergics like ipratropium bromide are less potent than beta-agonists and are used along with short-acting bronchodilators in severe asthma and in exacerbations, to improve lung function and reduce hospitalization.

Inhaled Corticosteroids

Inhaled corticosteroids are the most potent and effective controller treatment for asthma and the cornerstone of good asthma control. ICS benefits include: (1) decrease in symptoms, (2) improvement of lung function, (3) decreased AHR, (4) reduction in asthma exacerbations and admission rates, (5) reduced need for prednisolone by 50%, and (6) decreased risk of mortality. Second generation ICSs, such as fluticasone propionate, mometasone furoate and budesonide are preferred due to their increased anti-inflammatory potency and decreased systemic bioavailability. Dose equivalence of different ICS is shown in **Table 5**.

Mild intermittent asthma can be managed by the use of low-dose ICS. More severe forms can be controlled by medium dose of steroids which are double (2X), while high doses are quadruple (4X), with the exception of flunisolide and triamcinolone which are triple (3X). The clinical benefits of ICS outweigh the side effects. When using other forms of steroids for allergic rhinitis and eczema, the cumulative dose of steroids should be taken into account.

Side effects of ICS include (i) Oral candidiasis—due to the propellant-induced mucosal irritation and local immunosuppression, which can be overcome by the use of a spacer and rinsing the mouth following use; (ii) Dysphonia—associated with

Table 5 Dose equivalence of inhaled corticosteroids

Drug	Low daily dose (µg)
Beclomethasone dipropionate HFA	100
Budesonide	100
Ciclesonide	80
Flunisolide	500
Flunisolide HFA	150
Fluticasone propionate HFA	100
Mometasone furoate	100
Triamcinolone acetonide	400

vocal cord myopathy, which is dose-dependent and seen only in high doses of ICS and oral steroids; and (iii) Growth suppression—A 1.1 cm transient growth retardation is reported in children on long-term ICS. However, no significant difference in adult height is reported.

Leukotriene Receptor Antagonists

Leukotrienes are the main mediators shown to produce inflammation, bronchospasm, airway edema and mucus secretion in children with asthma. Montelukast, zafirlukast and pranlukast are the leukotriene receptor antagonists used in children. LTRAs are shown to effectively reduce symptoms, acute exacerbations and improve lung function. However, they are recommended as the second choice to ICS in many guidelines or as an add-on

therapy to ICS. Their efficacy is reported to be better in exercise-induced asthma and in the presence of rhinitis with asthma. ICS is shown to improve lung function by 5–15% and LTRA by around 2–7.5%. LTRAs have no significant side effects reported other than case reports of Churg Strauss-like vasculitis and behavioral symptoms. Zileuton is another drug which acts by leukotriene synthesis inhibition. However, it is licensed for use only in children more than 12 years, and needs to be used four times a day. Hence, it is not widely used for the management of asthma in children.

Long-acting Beta-2 Adrenergic Agonists in Combination with Inhaled Corticosteroids

Long-acting beta-2 adrenergic agonists (LABAs) such as salmeterol and formoterol are beta-agonists which are not routinely used as reliever medication. The onset of action of salmeterol is around 1 hour, whereas formoterol acts within 10 minutes, with an action lasting for 12 hours in both. It is well established that LABAs should be used always in combination with ICS and are licensed for use only in children more than 5 years. Formoterol is shown to have a fast action and, hence, a strategy of using a single inhaler for both control and reliever medication is proposed. Side effects of LABA include an increase in severe exacerbations and sudden death, especially when not used in conjunction with ICS.

Omalizumab

Immunoglobulin E binds to allergens and triggers the release of substances from mast cells and basophils that can cause inflammation. Omalizumab is a humanized monoclonal antibody that specifically binds to free IgE in the blood, thereby preventing antibodies from binding to IgE receptors on mast cells and basophils. As a result, these cells do not release histamine and other inflammatory substances, thereby preventing an allergic reaction and inflammation. Omalizumab is licensed for use in children more than 12 years of age with moderate to severe asthma, documented hypersensitivity to aeroallergens and in refractory cases of allergic asthma unresponsive to ICS. The dosage is determined by baseline IgE before start of treatment and body weight. It is given every 2–4 weeks subcutaneously.

Other Medications

Theophylline acts as a bronchodilator as well as anti-inflammatory due to its phosphodiesterase inhibitory action. It is not recommended as a controller medication in children due to its narrow therapeutic index, serious side effects and need to monitor blood levels. Cromolyn sodium and nedocromil are chromones which are nonsteroidal anti-inflammatory drugs known to stabilize mast cells. They are less effective than ICS, but have fewer side effects and are not easily available in India.

Choice of Drug Delivery Devices

Medications in asthma can be delivered by nebulizers, metered dose inhalers (MDI) or dry powder inhalers (DPI). A spacer is recommended for all MDI medications, as it overcomes the need for coordination of breathing, improves drug delivery to the lower airways and reduces oral thrush. Ideal method of using the spacer would be to emit a puff from the MDI into the spacer, followed by a slow inhalation and then a 5–10 sec breath hold. Alternatively, in younger children, following a puff, wait for regular tidal breathing of 30 sec or 10 breaths. DPI devices are breath actuated and the medication is delivered following a deep inspiratory breath with adequate flow. Rinsing of the mouth following use of MDI or DPI containing ICS is recommended to prevent development of oral thrush and reduce systemic absorption from the buccal mucosa.

Control of Asthma

On initiation of asthma treatment, patients are regularly monitored and assessed for control. Definition of asthma control in school-aged children is outlined in **Box 2**. Classification based on control is more dynamic, clinically relevant and helps to guide therapy. They include well controlled, partly controlled and uncontrolled (**Table 6**). Based on achieving control, treatment is either stepped up or stepped down.

Vaccination in Asthmatics

Indian Academy of Pediatrics (IAP) recommends influenza vaccination for severely asthmatic children and parents should be counseled regarding the benefits of preventing serious forms of influenza in these children. Other respiratory vaccines, such as the different pneumococcal vaccines are optional.

ACUTE SEVERE ASTHMA

Asthma exacerbation is defined as an acute or subacute episode of progressive increase in asthma symptoms, associated with airflow obstruction. Status asthmaticus is defined as severe asthma that necessitates hospitalization and fails to respond to initial treatment with inhaled beta-2 agonists and oral or IV steroids. Asthma attacks or exacerbations can be of varying severity, from mild to life-threatening. Clinical signs suggestive of acute severe asthma and life-threatening asthma are outlined in **Box 3**.

Assess the Severity of Exacerbation

The severity of asthma exacerbation can be estimated using the Becker's asthma severity score (**Table 7**). Asthma training module of IAP recommends a similar score. The same score is also used in facility-based Integrated Management of Neonatal and Childhood Illness (IMNCI) (**Table 8**). Based on the severity, an exacerbation

Table 6 Asthma control in children less than 5 years (Derived from GINA under-5, 2009)

Characteristics	Well controlled (all of the following)	Partly controlled (any measure present)	Uncontrolled (three or more features of partly controlled)
Daytime symptoms, wheezing, cough, difficult breathing	None or less than twice/week	More than twice/week (lasts for minutes and relieved rapidly by bronchodilators)	More than twice/week (lasts for hours and recurs, partly relieved by bronchodilators)
Limitation of activities	None	Any (may cough, wheeze or difficult breathing during play, exercise or laughing)	Any (may cough, wheeze, difficult breathing during play, exercise or laughing)
Nocturnal symptoms/awakening	None	Any (coughs during sleep or wakes up with cough, wheezing or difficult breathing)	Any (coughs during sleep or wakes up with cough, wheezing or difficult breathing)
Need for reliever/rescue treatment	Less than twice/week	More than twice/week	More than twice/week

BOX 2 Definition of asthma control in school-aged children

- Absence of daytime symptoms
- Absence of awakening at night due to symptoms
- No exacerbations
- No need for use of reliever medication
- No functional limitations in physical activity or exercise
- FEV₁ > 80% of predicted
- Minimal side effects on medication.

Abbreviation: FEV₁, forced expiratory volume in one second.

BOX 3 Clinical signs suggestive of acute severe and life-threatening asthma*Acute severe asthma*

- SpO₂ < 92% and/or PEF 33–50% and
- Cannot complete sentences in a single breath
- Breathless on feeding
- Pulse rate > 125 (> 5 years) and > 140 (2–5 years) per minute
- Respiratory rate > 30 (> 5 years) and > 40 (2–5 years) per minute

Life-threatening asthma (Red flag signs)

- SpO₂ < 92% and/or PEF 33–50%
- Hypotension and/or bradycardia
- Fatigue and exhaustion with increasing use of accessory muscles
- Silent chest
- Poor respiratory efforts
- Cyanosis
- Confusion or altered sensorium
- Dyspnea.

Abbreviations: PEF, peak expiratory flow; SpO₂, oxygen saturation.

Table 7 Becker's asthma severity score

Score	Respiratory rate/minute	Wheezing	Inspiratory: Expiratory ratio	Accessory muscle use
0	< 30	None	1:1.5	None
1	30–40	Terminal expiration	1:2	1 site
2	41–50	Entire expiration	1:3	2 sites
3	> 50	Inspiration and entire expiration	> 1:3	3 sites or neck strap use

Interpretation:

- Score > 4—moderate asthma; requires hospital admission
- Score > 7—severe asthma; requires pediatric intensive care unit (PICU) admission

can be managed at home, clinic, wards or intensive care units (ICUs). Management of asthma exacerbation at home is outlined in **Box 4**.

Oxygen saturation (SpO₂) less than 92% indicates a need for hospitalization. An arterial blood gas (ABG) should be obtained at baseline and monitored subsequently. Partial pressure of oxygen dissolved in arterial blood (PaO₂) less than 60 mm and normal or increasing partial pressure of carbon dioxide (PCO₂) more than 45 mm indicates respiratory failure and requires ICU admission and possible intubation with mechanical ventilation.

Hospital Management of a Severe Asthma Exacerbation

- *Airway, breathing and circulation* are established as with every other emergency. Intravenous access, continuous pulse oximetry and regular cardiorespiratory monitoring are initiated. Sedation is strictly avoided.

Table 8 Pulmonary severity score for acute severe asthma (Asthma Training Module, Indian Academy of Pediatrics)

Score	Respiratory rate/minute		Wheezing present*	Accessory muscle usage
	< 6 years	> 6 years		
0	< 30	< 20	None	No apparent activity
1	30–40	21–35	Terminal expiration with stethoscope	Questionable increase
2	41–50	36–50	Entire expiration with stethoscope	Increase apparent
3	> 50	< 50	During inspiration and expiration without stethoscope	Maximum activity
Add Score	0–3 Mild 4–6 Moderate > 6 Severe		*If wheezing absent (due to minimal) air flow), score = 3	

BOX 4 Home management of acute asthma exacerbations

- All parents are instructed to strictly follow a written *Asthma Action Plan* as it is shown to reduce the risk of death by 70%
- Rescue medication with 2–4 puffs of short-acting bronchodilators using MDI with spacer given at 3–5 min gaps, repeated at 20-min intervals in first hour is initiated
- Response is monitored for resolution of symptoms within 1 hour and no signs or symptoms after 4 hours
- In case of no response with short-acting bronchodilators, an oral steroid can be started at 1–2 mg/kg which should be maintained for 3–4 days
- The child needs to be transferred to the hospital immediately where:
 - There is no improvement after 10 puffs of short-acting bronchodilator
 - Deterioration despite optimal treatment
 - Risk factors for mortality—red flag signs and life-threatening asthma
- Oxygen with nebulized salbutamol is given during transport
- Monitor pulse rate, respiratory rate, use of accessory muscles of respiration, degree of wheezing, degree of agitation and level of consciousness.

Abbreviation: MDI, metered dose inhalers.

- *Oxygen* is administered via nasal cannula or mask. Children with SpO₂ less than 94% need to be treated with high-flow oxygen via mask or nasal cannula until levels more than 95% are attained. In severe cases, PCO₂ also needs to be monitored to look for impending respiratory failure.
- *Fluids*: Usually normal fluids are needed. In cases with severe distress, normal saline to restore euvoolemia or Ringers lactate to correct dehydration may be needed. Serum electrolytes, especially potassium needs to be monitored when systemic beta-2 agonists are being used.
- *Inhaled beta-2 agonists* are the cornerstone of management in asthma. In mild to moderate cases, an MDI with spacer is preferred. LABAs should be discontinued in cases where relievers are required every 4 hourly. Two to four puffs of salbutamol (100 µg each) every 20 min are given via MDI spacer for the first 1 hour. Instead, one could use three doses of nebulized salbutamol at a dose of 0.15 mg/kg at 20 min interval as well. In severe cases, back-to-back salbutamol nebulization can also be used. Continuous nebulization at 0.15–0.5 mg/kg/hour or 10–20 mg/hour is superior to intermittent doses in children, who require frequent nebulization.
- *Systemic steroids* are recommended early in acute severe asthma. Different guidelines recommend 1–2 mg/kg/day for

3–5 days. This approximately amounts to 10 mg in children less than 2 years, 20 mg in 2–5-year olds and 40 mg in more than 5-year olds. Those on maintenance oral steroids should receive 2 mg/kg up to a maximum of 60 mg. No tapering doses are needed. In children who vomit, a repeat dose of steroid or IV steroids can be considered with hydrocortisone at 10 mg/kg stat followed by 4–5 mg/kg thrice daily.

- *Anticholinergics* such as ipratropium bromide (250–500 µg/dose) can be alternated with nebulized beta-2 agonists in children refractory to initial therapy. Three doses can be repeated every 20 min followed by every 6 hourly.
- *Intravenous magnesium sulfate* ($MgSO_4$) inhibits calcium uptake and subsequently causes smooth muscle relaxation and reduces histamine-induced airway spasm. $MgSO_4$ can be utilized in patients who fail to respond to frequent inhaled beta-agonists and systemic corticosteroids. Doses used include a 50 mg/kg/dose over 30 min or a continuous infusion at 10–20 mg/kg/hour. It is repeated every 4–6 hourly. Complications include hypotension, cardiac arrhythmias, central nervous system depression and flushing with high-serum magnesium levels (> 10 – 12 mg/dL).
- *IV beta-2 agonists* are used in patients unresponsive to continuous inhaled therapy. Terbutaline which is widely available is given as a 10 µg/kg bolus over 10 min followed by a continuous infusion at 0.1–10 µg/kg/min. Subcutaneous terbutaline at 0.01 mg/kg/dose (maximum of 0.3 mg) is used in the absence of IV access.
- *Heliox*, a mixture of 80% helium and 20% oxygen, is a specialty gas that can decrease airway resistance in obstructed airways. It may be useful for the severely ill patient in an ICU setting.
- *Mechanical ventilation* in severe asthma is indicated in the following situations: (1) cardiorespiratory arrest; (2) rapid deterioration of mental state; (3) severe hypoxia with rising PCO_2 ; or (4) poor response to initial medication. Ventilation strategies aim to minimize hyperinflation and air-trapping, which include slow ventilator rates with prolonged expiratory phase, short inspiratory time and minimal positive end-expiratory pressure (PEEP). Adequate oxygenation, permissive hypercarbia and arterial pH more than 7.2 is maintained.

LONG-TERM OUTCOME OF CHILDHOOD ASTHMA

The outcome of childhood asthma can be evaluated in terms of asthma symptoms, such as wheezing and asthma attacks, by presence of obstruction on lung function assessment or by AHR.

While the prevalence of asthma is greater in boys in childhood, asthma is more prevalent in women in adulthood. Remission of symptoms sometimes occurs during puberty, particularly in boys. Risk factors in childhood which predispose to persistent symptoms in adulthood include severe childhood asthma, later age at onset, female gender, atopy, allergic rhinitis and lower lung function. However, with contemporary asthma treatment and care, most asthmatic individuals are able to lead a normal, healthy life.

IN A NUTSHELL

1. Childhood asthma most often starts before school age and is increasing in prevalence across the world.
2. All that wheezes is not asthma. Likewise, isolated cough without wheeze or chronic wet cough needs evaluation.
3. Allergic rhinitis, GERD and sinusitis are common comorbid conditions and, if present, require concurrent treatment.
4. Spirometry is an integral component of asthma management.
5. Inhaled corticosteroids are the mainstay in the treatment of childhood asthma.
6. Strict adherence to an asthma action plan reduces exacerbations, morbidity and mortality.

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Chapter 39.20

Aerosol Therapy

Bruce K Rubin, Ronald W Williams

Aerosol therapy has been used for thousands of years with the burning and inhalation of tobacco and herbs. Aerosols have been an integral part of Ayurvedic medicine and are a cornerstone of modern therapy for airway diseases. Aerosol therapy allows targeting the airways often better than can be achieved by systemic administration. Because of the blood airway barrier, many medications either remain at the airway or are inactivated after uptake and thus their systemic side effects can be minimized.

Aerosol medication's formulation, stability and the requirement for airway tolerability are important for their efficacy and safety. Only medications that have been designed to be administered as an aerosol, and tested for safety and effectiveness when delivered by inhalation should be used by this route. It may be dangerous to take medications intended for intravenous (IV) administration and to nebulize these for inhalation.

There are also novel applications for aerosol therapy, including acinar deposition for systemic administration of proteins and peptides (e.g., insulin), devices for administering aerosols to the paranasal sinuses, engineered particles targeting cancer chemotherapy to involved airways, and also for immunization, gene transfer and delivering biologics through the airway. The focus of this chapter will be on the more commonly used medications for respiratory diseases.

WHAT IS AN AEROSOL?

An aerosol is a group of particles that remain suspended in air because of a low terminal settling velocity. The terminal settling velocity of an aerosol is determined by the aerodynamic size, usually denoted as the particle mass median aerodynamic diameter (MMAD), which is a function of the size, geometry and density of the particle. In practical terms, larger and heavier particles that are inhaled quickly are more likely to settle in the mouth than in the lung. Particles with MMAD less than 2 μm are exhaled unless there is a breath hold. Those larger than 5–10 μm preferentially deposit in the oral pharynx, or are never effectively nebulized.

MMAD describes the median particle size, but ignores size variability. Particle size distribution is described by the geometric standard deviation (GSD). When GSD is less than 1.22, this is a monodisperse. Most medications for therapeutic administration are heterodisperse. A larger GSD means fewer particles will be in the respirable mass, i.e., the proportion of particles with 2–5 μm MMAD. Different devices can produce aerosols with the same MMAD but different GSD, and thus number of particles that are available for the patient to inhale may vary a lot.

AIRWAY DEPOSITION

Particles are deposited in the airway by inertia, sedimentation, and Brownian diffusion. Large particles with high inertia impact in the mouth, increasing side effects while limiting lower airway deposition and therapeutic benefit. Impaction can be reduced by decreasing the MMAD of the particle or by decreasing inspiratory flow. High inspiratory flow will produce turbulence, which, in turn, dramatically increases impaction. Sedimentation is enhanced by allowing time for particles to settle on the airway after inhalation. This requires very low flow and is the reason why a breath hold is recommended after inhaling an aerosol. Brownian motion affects the smallest of particles and often these are exhaled. Particle

deposition in the lower airway is increased when aerosols are inhaled slowly and deeply, followed by a breath hold. A corollary to this is that there is almost no pulmonary deposition of an aerosol given to a crying baby or child. It is important to know that in severe airway disease, there is inhomogeneous ventilation leading to preferential deposition of medication at sites where airways are patent, which are often the less severely involved airways.

DEVICES

Many devices have been used for aerosol administration. The most commonly used are jet nebulizers, pressurized metered dose inhalers (pMDIs) and dry power inhalers (DPIs). It is important that devices be used correctly, and that patients are taught their operation by a knowledgeable practitioner. It is also important that this be checked each time the patient returns for clinic visits.

Jet Nebulizers

Jet nebulizers operate by the Venturi principle, where particles are pulled into the airstream for inhalation. Air flow must be fast enough (at least 8 LPM) to produce particles with an appropriate MMAD, and there should be minimal residual volume remaining after the medication has been nebulized. Inexpensive nebulizers often generate low flows and leave large residual volumes, thus producing poorly effective aerosol therapy. Overall, nebulizers are inefficient, as even the best jet nebulizers give no more than 15% deposition in the airway. This is why much more medication must be administered when a jet nebulizer is used (in mg) as compared with a pMDI or DPI (in μm).

Nebulizers should not be used when a child is crying or distressed, nor should they be placed in front of the face (so called *blow by*) as either will decrease the amount of medication inhaled to almost nothing. Whenever possible, aerosol from a jet nebulizer should be inhaled using a mouthpiece, as this doubles the amount of medication when compared to using a mask. Nearly all children over the age of 3 years can use a mouthpiece when trained. A critical problem with jet nebulizers is that adherence to therapy is much worse as compared to other devices. Presumably this is due to the time it takes to set up the device, administer the medication and clean the device after each use.

Jet nebulizers are more effective for aerosolizing solutions than suspensions, but many of the inhalational corticosteroids (ICs) are suspensions. The result is often delivery of less than 2% of the dose to infants and small children. Because the total volume of particles inhaled increases as the child grows, there is no need to adjust the amount of medication given based on the child's weight. This is true for jet nebulizers, pMDIs and DPIs.

To reduce medication wastage, there are breath-activated nebulizers that only flow when the patient inhales, but there must be a sufficient inspiratory flow to trigger the valve. Vibrating mesh nebulizers produce a more uniform particle size and operate without an external air source. Because the mesh can be clogged by viscous or hypertonic solutions, it is important that these devices *only* be used with the drugs that were intended.

Pressurized Metered Dose Inhalers

The pMDI was developed nearly 60 years ago and has undergone only minor changes. Medication is metered into a valve, and released when the canister is depressed in the boot. This is then inhaled slowly and deeply into the lungs. Pulmonary deposition can be improved and oral deposition and side effects can be decreased by always pairing a pMDI with a valved holding chamber (VHC). A spacer is a hollow tube that gives the aerosol plume time to mature before inhalation. When using a spacer, it is important to time inhalation with actuation of the pMDI. A VHC is a spacer

with a one-way valve at the inhalation orifice so that medication remains suspended in the chamber until the patient inhales. Data show aerosol medications, such as salbutamol or ICS, are more effective and have fewer side effects when given by pMDI and VHC than by jet nebulizer. This is true even in the youngest of children, and even for children in the critical care unit.

Dry Powder Inhalers

Dry powder inhalers produce a fine powder of medication usually from scraping a reservoir or having individual doses encapsulated and punctured before inhalation. Because the medication must be dispersed to form the aerosol, lactose is often added as a carrier, and a minimum peak inspiratory flow is needed. Low resistance devices like the Diskus[®] (GSK) require only 30 LPM inspiratory flow for dispersion while higher resistance devices, e.g., the Turbuhaler[®] (Astra), require greater than 60 LPM inspiratory flow. Children under the age of 6 years may find it difficult to achieve such flow rates, and the high flow can also lead to proximal deposition of medication.

DPIs are intrinsically breath-activated, as patients do not get medication until inhalation begins. Once a DPI is primed, the medications should be inhaled immediately as there is a risk of spilling the drug if tipped downward before inhalation. High humidity can cause the dry particles to stick together and clog the flow channel. This can happen with ambient high humidity or when the patient exhales into the device.

Nasal Delivery

The paranasal sinuses and nose can also benefit from aerosol medications. Typical nasal pumps have been used to deliver antihistamines, decongestants and ICS to the nasopharynx but these do not deliver medication to the sinus cavities. Recent devices using pulsatile aerosol flow or sound waves have made sinus delivery possible.

AEROSOLIZED DRUGS

The most common use of aerosol medications has been in the treatment of asthma. The beta agonist bronchodilators are effective and easily administered as a solution by nebulization or as a pMDI. Medication delivery is faster, and costs and side effects are less, when using pMDI with VHC or else a DPI. This is true even in an emergency setting or in the critical care unit.

Cystic fibrosis (CF) is a condition of chronic airway infection, inflammation and secretion retention. There is almost no true mucus in the CF airways; these secretions are full of polymeric deoxyribonucleic acid (DNA) more characteristic of pus than mucus. Thus, typical mucolytics, like N-acetylcysteine (NAC) are ineffective for treating CF. Dornase alfa (Pulmozyme, Genentech) aerosol can depolymerize the abnormal DNA network. While effective in CF, dornase has been shown to worsen lung function in persons with non-CF bronchiectasis. The expectorants, hypertonic saline aerosol and DPI mannitol have been used to treat CF by drawing water into the periciliary fluid unbinding secretions from the epithelium and inducing an effective cough. Because these medications can produce bronchospasm, a short-acting bronchodilator like salbutamol should be administered first.

Aerosol antibiotics have also been developed for treating airway infection in CF. Although high levels of antibiotics, far exceeding the MIC₉₀, are deposited in the proximal airway, the antibiotic concentration rapidly decreases in distal airways and this can induce resistance. Therefore many of these antibiotics are given on

alternate months so that bacteria can again become susceptible. Antibiotics currently available are tobramycin, aztreonam and colistin. These are concentration dependent medications and thus aerosolized cephalosporins or penicillins are not recommended.

Other Aerosols

Bland aerosols have no place in the treatment of airway disease as these do not improve mucus clearance or hydration. Similarly, sodium bicarbonate inhalation is irritating to the airway and should not be used; it is ineffective as a mucoactive medication. Although NAC is available for nebulization, it is also irritating to the airway with pKa 2.2 and a foul odor. There are no published data showing that aerosol NAC improves the course of any lung disease, and, therefore, we recommend that it should not be used in children.

ADHERENCE TO THERAPY

Although research has brought us excellent medications and highly effective aerosol devices, the key to effective therapy is adherence. This first requires that the caregiver and patient understand proper use of the medication and device. Education should be provided by a knowledgeable practitioner, and should be ongoing. Handing a patient an aerosol device without a demonstration is a recipe for therapeutic failure.

Some forms of therapy produce better adherence than others. Bronchodilators give a sensation of immediate relief and tend to be used more consistently than ICs. As mentioned earlier, we rarely use jet nebulizers because adherence is so much worse than with other forms of aerosol therapy. The key to effective aerosol therapy is to understand the device, teach it well, and ensure that the patient is using it correctly.

IN A NUTSHELL

1. Particles with mass median aerodynamic diameter (MMAD) between 2 μ m and 5 μ m are best suited for aerosol therapy.
2. It is dangerous to nebulize medications intended for IV administration for inhalation therapy.
3. Aerosol medications, such as salbutamol or inhaled corticosteroids are more effective and have fewer side effects when given by pMDI and VHC than by jet nebulizer.
4. Aerosol antibiotics have also been developed for treating airway infection in cystic fibrosis.
5. There are no published data showing that aerosol N-acetylcysteine improves the course of any lung disease, and, therefore, we recommend that it should not be used in children.
6. The key to effective aerosol therapy is to understand the device, teach it well, and ensure that the patient is using it correctly.

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Chapter 39.21

Pneumonia

Swati Dublish, Varinder Singh

Pneumonia is an inflammation of the parenchyma of the lungs. Usually pneumonia is caused by microorganisms; however, noninfectious causes include aspiration of food or gastric acid, foreign bodies, hydrocarbons, and lipid substances, hypersensitivity reactions, and drug- or radiation-induced pneumonitis. The present chapter focuses on pneumonia resulting from acute infections.

EPIDEMIOLOGY

Acute respiratory infections (ARI) encompass viral and bacterial infections of the respiratory tract. The Third National Family Health Survey (NFHS-3) data suggests that as many as 6% children under age of 5 years in India showed symptoms of ARI at some time in the 2 weeks preceding the survey. While upper respiratory infections are often self-limiting, lower respiratory infections, in particular, pneumonia, pose life-threatening situation. Most pneumonia deaths are caused by bacteria. Pneumonias are the number one cause of under-5 child mortality, responsible for nearly 400,000 deaths in India annually. These deaths can be prevented by appropriate treatment with antibiotics. Pneumonia can be distinguished from other respiratory tract infections by the use of simple clinical signs, such as respiratory rate and lower chest in-drawing.

DEFINITIONS

There are several ways in which pneumonia can be defined. From *pathological viewpoint*, pneumonia results from invasion of lungs by an infectious agent which may start an inflammatory response and ensuing damage may involve airways, alveoli, connective tissue, visceral pleura and vascular structures. A more *practical definition* of pneumonia will include fever, respiratory symptoms, and evidence of parenchymal involvement by either physical examination or the presence of infiltrates on chest radiography. Most experts define pneumonia as association of clinical findings with radiographic evidence of infiltrates. Since in many developing countries and also in many peripheral settings, radiological services may not be easily available, a more pragmatic term, lower respiratory tract infection (LRTI), is used wherein the diagnosis is made on the basis of simple clinical signs (e.g., fast breathing). This simple definition cannot and does not make any distinction between viral bronchiolitis, croup, asthma and pneumonia.

CLASSIFICATION OF PNEUMONIA

Pneumonia may be classified as simple and complicated pneumonia. Simple pneumonia can be bronchopneumonia—patchy involvement of the lung, which can be unilateral or bilateral; and lobar pneumonia—which involves almost whole of a single lobe. Complicated pneumonia refers to a situation where the pulmonary parenchymal infection is complicated by parapneumonic effusions, empyema, necrotizing pneumonia abscesses or cavities, pneumothorax or bronchopleural fistula.

Given the difficulties in making an etiological diagnosis, pneumonia etiology is often inferred from epidemiology. Therefore, another reasonable classification is *community acquired pneumonia (CAP)* and *hospital acquired pneumonia (HAP)*. CAP is defined as the presence of signs and symptoms of pneumonia in a

previously healthy child due to an infection contracted outside of the hospital, i.e., child should not have been hospitalized within 14 days prior to the onset of symptoms, or has been hospitalized less than 4 days prior to onset of symptoms. HAP can be early-onset and late-onset. Early HAP is a pneumonia occurring within the first 4 days of hospitalization and is more likely due to antibiotic-sensitive bacteria. It usually carries a better prognosis. Truly, early onset HAP is a misnomer as definition of CAP covers it adequately. Late-onset HAP (occurring 5 days or more after admission) is more likely nosocomial; due to polymicrobial and multidrug-resistant pathogens; and is associated with increased patient mortality and morbidity.

A typical pneumonia occurs with acute onset of fever, cough and rapid breathing while few can have a more gradual onset associated with low-grade fever or no fever, headache, nonproductive cough and malaise, which is referred to as atypical pneumonia.

PATHOGENESIS

Most pulmonary pathogens are transmitted from person to person by droplet infection. Bacteria may be transmitted by inhalation or microaspiration. Droplet particles larger than 10 μm are usually large enough to be deposited in the pharynx, whereas those from 3 μm to 10 μm may lodge in the larger airways while particles between 0.5 μm and 3 μm reach the alveolar surface. Viruses are among the common causes of pneumonia in early infancy. Most of the children are infected with the respiratory viruses but only few develop pneumonia.

Any breach in the normal defense mechanisms against pneumonia in the body like altered mucociliary clearance or cough reflex or humoral and cellular immunity, or an obstructed airway predisposes to pneumonia. The risk factors predisposing to pneumonia are detailed in **Table 1**, whereas **Table 2** details risk factors associated with increased mortality due to pneumonia.

The pathogenesis of pneumonia is variable. The classical stages of lobar pneumonia (especially pneumococcal) include congestion, red hepatization, gray hepatization and resolution (**Flow chart 1**). In viral pneumonia, there is infection of the perialveolar cells leading to thickening of alveolar walls. This leads to occlusion of alveolar space with exudates, slough and activated macrophages, leading to poor gas exchange. In many cases, there may be inflammation of the bronchioles leading to air trapping and contributing to poor gas exchange. In interstitial pneumonia, the walls of the alveoli and interstitial septae are involved, and the alveolar space is spared. The interstitial infiltrate predominantly includes lymphocytes, macrophages and plasma cells.

ETIOLOGY

In pediatric age group, the developing immunity and age-related exposures result in infection caused by varied yet consistent set of bacterial and viral pathogens. The potential pathogens are, therefore, defined separately for each age group (**Table 3**). The pneumonia in neonatal period is mostly caused by group B streptococci or gram-negative enteric bacteria.

Viruses are among the frequent pathogens in children younger than 2 years. Of the viral pathogens, respiratory syncytial virus (RSV) is detected in up to 40% of children younger than 2 years. Other viruses detected are adenoviruses, influenza A and B viruses, bocavirus, human metapneumovirus, parainfluenza viruses, coronaviruses and rhinovirus. RSV and influenza virus infections commonly predispose infants and young children to bacterial infections. *Chlamydia trachomatis* is an important pathogen in infants between 3 weeks and 19 weeks of age.

Among the bacterial causes of pneumonia in young children, *Streptococcus pneumoniae* is most common (30–50% cases), followed by *Haemophilus influenzae* (10–30% cases),

Table 1 Risk factors for the development of pneumonia

Definite risk factors	Likely risk factors	Possible risk factors
<ul style="list-style-type: none"> • Malnutrition • Low birthweight • Lack of exclusive breastfeeding during the first 4 months • Lack of measles immunization • Indoor air pollution • Overcrowding 	<ul style="list-style-type: none"> • Parental smoking • Zinc deficiency • Maternal inexperience • Underlying comorbid conditions: <ul style="list-style-type: none"> – Congenital heart disease – Esophageal obstruction or dysmotility, e.g., vascular rings, tracheoesophageal fistula – Gastroesophageal reflux disease – Mucociliary dysfunction, e.g., cystic fibrosis, primary ciliary dyskinesia – Neuromuscular disorders – Asthma – Immunodeficiency (congenital or acquired) – Diabetes mellitus – Bronchopulmonary dysplasia and chronic lung disease – Sickle cell disease 	<ul style="list-style-type: none"> • Maternal illiteracy • Day-care attendance • Rainfall (humidity) • High altitude (cold air) • Vitamin A deficiency • Higher birth order • Outdoor air pollution

Table 2 Risk factors of mortality in children with severe pneumonia

<ul style="list-style-type: none"> • Age less than 6 months
<ul style="list-style-type: none"> • Head nodding
<ul style="list-style-type: none"> • Altered sensorium
<ul style="list-style-type: none"> • Inability to feed
<ul style="list-style-type: none"> • Pallor
<ul style="list-style-type: none"> • Severe malnutrition
<ul style="list-style-type: none"> • Concomitant diarrhea or other underlying comorbid illnesses like congenital heart disease

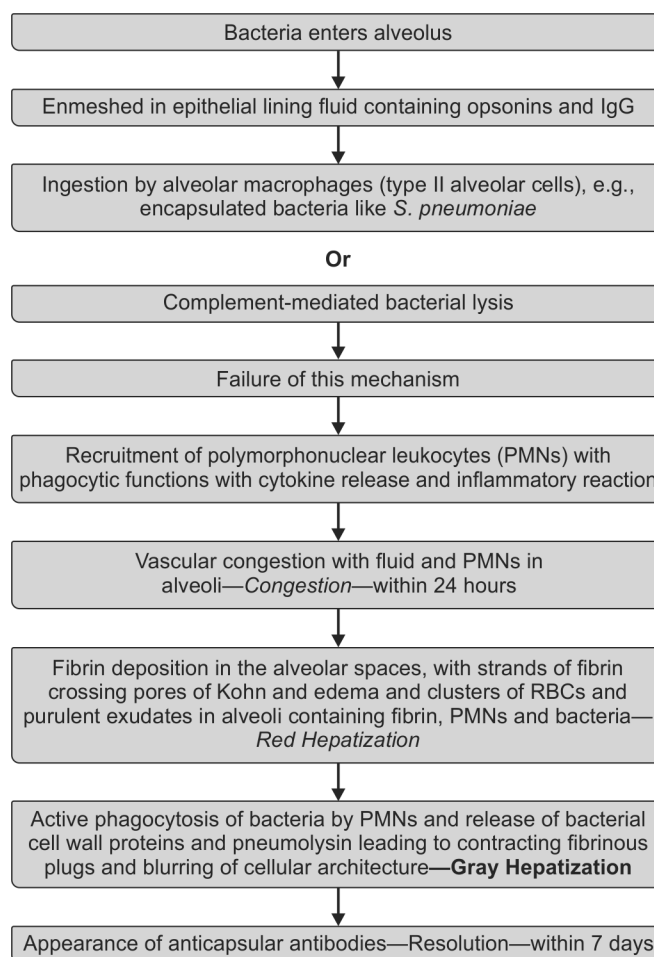
Staphylococcus aureus and *Klebsiella pneumoniae*. Multiple serotypes of *S. pneumoniae* are present with different prevalence rates. According to a serotyping study done in India, among 150 clinical isolates from invasive and life-threatening pneumococcal infections, 59.3% belonged to serotypes 1, 6, 19, 5, 23 and 7. Serotype 1 was the most common isolate in meningitis and empyema. According to another study, among 42 pneumococcal strains, over one-third in children and nearly half in adults were serotypes 5, 6 and 7. The remaining 11 of 14 strains in children and 20 of 28 strains in adults belonged to 8 serogroups/types, namely 3, 4, 10, 11, 12, 13, 19 and 20. Prevalence of penicillin resistance is currently reported to be low in most of the countries.

Among severely malnourished children, *K. pneumoniae*, *S. pneumoniae*, *Escherichia coli*, *S. aureus* and *H. influenzae* are common organisms. Other bacterial infections like *Bordetella pertussis* and *Mycobacterium tuberculosis* should also be considered in differential diagnosis.

Fungal pneumonia (due to *Histoplasma*, *Coccidioides*, *Blastomyces* and *Cryptococcus*) in normal immunocompetent hosts is uncommon.

CLINICAL FEATURES

Children with pneumonia usually present with fever, tachypnea, cough, abdominal and/or chest pain. In pneumonia caused by atypical pathogens, a more gradual onset associated with low-grade fever or no fever, headache, nonproductive cough and malaise may be present. The presence of wheezing is more often seen in younger children though may be more often associated with a nonbacterial pathogen. Tachypnea is a simple yet fairly specific and sensitive sign for pneumonia if asthma and bronchiolitis have been excluded (**Table 4**). In infants with pneumonia, tachypnea

Flow chart 1 Pathogenesis of lobar pneumonia

may correlate with hypoxemia. Other causes of tachypnea could be fever, dehydration or metabolic acidosis. Intercostal, suprasternal or subcostal retractions indicate severe pneumonia. Nasal flaring and *head bobbing* have also been statistically associated with hypoxemia. Fever is the most sensitive sign while grunting and retractions are the most specific signs corresponding to presence of alveolar infiltrates on chest radiograph. In the absence of cough, possibility of pneumonia is very low.

Table 3 Common etiological agents causing community-acquired pneumonia in different age groups

Newborns and young infants < 3 months	3 months to 5 years	Older than 5 years
<ul style="list-style-type: none"> • Group B <i>Streptococcus</i> • Enteric gram-negative bacilli • <i>Streptococcus pneumoniae</i> • <i>Haemophilus influenzae</i> • <i>Chlamydia trachomatis</i> • Group D streptococci • <i>Listeria</i> spp. • Anaerobes 	<ul style="list-style-type: none"> • Adenoviruses • Bocavirus • Human metapneumovirus • Influenza A and B viruses • Parainfluenza viruses • Coronaviruses • Rhinovirus <i>Streptococcus pneumoniae</i> • <i>Haemophilus influenzae</i> • <i>Staphylococcus aureus</i> • <i>Bordetella pertussis</i> 	<ul style="list-style-type: none"> • <i>S. pneumoniae</i> • <i>S. aureus</i> • <i>M. pneumoniae</i>

Table 4 Age-specific respiratory rates as per World Health Organization (WHO)

Age	Respiratory rate
< 2 months	≥ 60/min
2–12 months	≥ 50/min
> 12 months–5 years	≥ 40/min

The clinical presentation of viral pneumonia may include tachypnea, retractions (supracostal, intercostal or subcostal) with or without nasal flaring. Low-grade fever is common; fever higher than 39.5°C (103°F) is uncommon. The presence of concomitant upper respiratory infection (rhinorrhea, sneezing or otitis media) supports a probability of a viral etiology, though these at times can be associated with superimposed bacterial infection. Mild to moderate dehydration may be present due to increased insensible losses and poor oral intake. Systemic toxicity is less common though influenza may lead to high fever and toxic appearance. Children can develop acute otitis media, sinusitis and bacterial tracheitis, febrile seizures, encephalitis or encephalopathy, myositis, myocarditis or Reye's syndrome during an episode of influenza pneumonia.

In atypical pneumonia due to mycoplasma, initial manifestation is pharyngitis followed by hoarseness of voice. Fever, usually low-grade, and cough are predominant symptoms; vomiting and diarrhea may be seen in up to 20% patients. Rhinitis is less common. Crepitations or wheezing may be audible on auscultation. The mean duration of illness is around 2 weeks, although cough may persist for more than a month. Mycoplasma infection may be associated with sinusitis, otitis media, myocarditis, pericarditis, mucocutaneous eruptions, hemolytic anemia, arthritis, glomerulonephritis, and nervous system diseases (aseptic meningitis, encephalitis, cerebellar ataxia, transverse myelitis, peripheral neuropathy, psychosis and Guillain-Barré syndrome).

Streptococcus pneumoniae is the most common bacterial pathogen causing pneumonia in children, responsible for more than 50% cases. The onset may be preceded by a mild upper respiratory tract infection, purulent unilateral conjunctivitis, or otitis media. In infants, a sudden high-grade fever accompanied by a seizure, and diarrhea or vomiting may be the earliest manifestations. Irritability, nasal flaring, rapid and shallow respirations, grunting, abdominal distention, perioral cyanosis, tachycardia and unilateral diminished respiratory excursion may be seen during the course of the illness. Cough may be absent as alveoli have few cough receptors. In the older child and the adolescents, the onset is abrupt and the patient may appear ill with high-grade fever along with chills or rigors, fever, headache, dyspnea, pleuritic pain and cough. Sputum production may be apparent in children older than 8–10 years of age. Occasionally,

signs and symptoms suggestive of bacterial pneumonia may be absent; fever may be the only sign.

Haemophilus influenzae B pneumonia is more common in children younger than 5 years of age, particularly in children under 2 years. *S. aureus* pneumonia presents as an acute and severe rapidly progressive illness. In almost 50% of cases, pneumatocele formation may occur due to destruction of bronchial walls leading to air-trapping. Empyema, pneumothorax and pyopneumothorax are common complications. It can also lead to pyemia and metastatic lesion in the pericardium, joint, muscles, etc. Many strains of community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) carry the gene for Panton-Valentine leukocidin, an exotoxin lethal to leukocytes and, therefore, leading to tissue necrosis, skin lesions, necrotizing pneumonia and necrotizing fasciitis. Group A *streptococcus* and *Streptococcus pyogenes* are infrequent causes of pneumonia, usually presenting with bacteremia and scarlet fever. Infection with measles, varicella and influenza predispose to coinfection from group A *streptococcus* because of impairment of host immunity.

Chlamydia pneumoniae infection usually occurs in children between the ages of 5 years and 15 years and the usual route of transmission is via respiratory secretions and fomites. The illness begins with a nonspecific prodrome of low-grade fever, malaise, sore throat, headache and cough. Patients may initially show signs of upper respiratory tract infections, such as pharyngitis, laryngitis or sinusitis later progressing to pneumonia or bronchitis. *C. pneumoniae* leads to an IgE-mediated bronchial reactivity. The physical examination of patients may show nonexudative pharyngitis, wheezes and fine or coarse crepitations. Pneumonia is more common in adolescents. Complications associated with chlamydia infection are pneumatocele, pneumothorax, interstitial fibrosis and lung abscess. Pleural effusion is uncommon. Other complications include erythema nodosum, reactive arthritis, Guillain-Barré syndrome, meningoencephalitis, myocarditis, and endocarditis. Chest X-rays show a single subsegmental lesion of only one lobe as the most common lesion, though alveolar infiltrates or subsegmental pneumonitis without consolidation may be seen.

It is difficult to distinguish viral from bacterial pneumonia on the basis of clinical features, radiology or laboratory investigations but presence of an upper respiratory catarrh, a lymphocytic predominance in leukocyte count is more likely in viral pneumonias. Radiological evidence of lobar, segmental, or rounded well-defined consolidation affecting a single lobe, large pleural effusion, abscess, bullae or pneumatoceles points to a possible bacterial etiology. Bacterial superinfection of a viral pneumonia can be suspected when there is an abrupt change in symptoms with appearance of generalized toxicity, marked and changed leukocytosis and new X-ray findings of parenchymal consolidation or pleural effusion.

COMPLICATIONS

The complications of pneumonia include parapneumonic effusions, empyema, necrotizing pneumonia, pneumatoceles, lung abscess and pneumothorax. The complications are to be suspected in cases not responding to treatment or showing deterioration.

DIAGNOSIS

Etiological Diagnosis

Early identification of the etiologic agent is important for all infectious diseases to provide a target-oriented and narrow spectrum treatment to rationalize the usage of antibiotics and minimize the emergence of drug resistance. However, the bacteriological diagnosis for pneumonia is neither routinely feasible nor useful as the yield is very low.

Blood culture positivity in children being treated as inpatients is around 8%. It is more likely to be positive in the presence of sepsis or organ dysfunction. The culture of respiratory specimens can be done but can have major drawbacks which limit their utility for any routine clinical use. Firstly, younger children are unable to expectorate; even when sputum is available, its contamination by the upper airway microbiome limits its utility; and lastly, the isolate may reflect the colonizing bacteria rather than the invading bacteria. It is worth remembering that many a common bacterial and viral pathogens may be carried in the respiratory passages of the normal population as well.

Gram stain and culture of induced or expectorated sputum can be attempted in older children (> 8 years old) and adolescents. Specimen produced by cough and containing excess squamous rather than epithelial cells indicates an upper tract origin. Specimens with more than 25 squamous cells per low-power field are not considered adequate. Other useful parameters are the presence of neutrophils and a monotonous or relatively monotonous morphology of the bacteria in the specimen. However, it is still difficult to differentiate the colonizing bacteria from the real culprit.

In adults, urinary antigen tests for the detection of *S. pneumoniae* correlate well with sputum culture and, therefore, are routinely used to diagnose pneumococcal pneumonia in adults. However, in children, positive results of pneumococcal urinary antigen test do not reliably distinguish infection from mere, colonization and are, therefore, not recommended.

Testing for viral pathogens can be done using nasopharyngeal aspirate for reverse transcription-polymerase chain reaction (RT-PCR), viral antigen detection or acute and convalescent sera for serology.

The diagnostic tests utilized for *Mycoplasma pneumoniae* infections include serology, cold agglutinating antibodies, culture and molecular-based methods, such as PCR assays. Serologic tests include complement fixation, enzyme-linked immunosorbent assays (ELISAs), and rapid enzyme immunoassay cards. Cold agglutinin titers more than 1:64 are present at the time of acute illness in adults but the test is less well studied in children. Serology is the primary means of diagnostic testing for *C. pneumoniae*. Confirmation of primary acute infection requires documenting an IgM titer of 1:16 or greater or a 4-fold rise in IgG titer between acute and convalescent serum specimens. In case of reinfection, IgM antibody may not appear, and the level of IgG antibody titer may rise quickly within 1–2 weeks of infection. The organism or its deoxyribonucleic acid (DNA) can also be directly identified by means of culture or PCR testing in specimens from nasopharyngeal or throat swabs, sputum, blood or tissue.

In children with severe or life-threatening pneumonia, invasive samples can be tried like bronchoscopy with bronchoalveolar lavage or brush biopsy, percutaneous lung aspiration (blind or computed tomography [CT] guided) or open lung biopsy. In

children who are mechanically ventilated, endotracheal aspirates for Gram stain and culture as well as for viral pathogens like influenza can be done.

Ancillary tests like complete blood count with WBC differential may help to guide therapy and also may give an indication regarding anemia or thrombocytopenia heralding hemolytic-uremic syndrome associated with pneumococcal infection. Acute phase reactants like C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and procalcitonin do not clearly distinguish bacterial from viral infection when used in isolation. Low values may be helpful in distinguishing viral pneumonia from bacterial pneumonia associated with bacteremia. Declining values of CRP or procalcitonin may correlate with improvement in clinical symptoms.

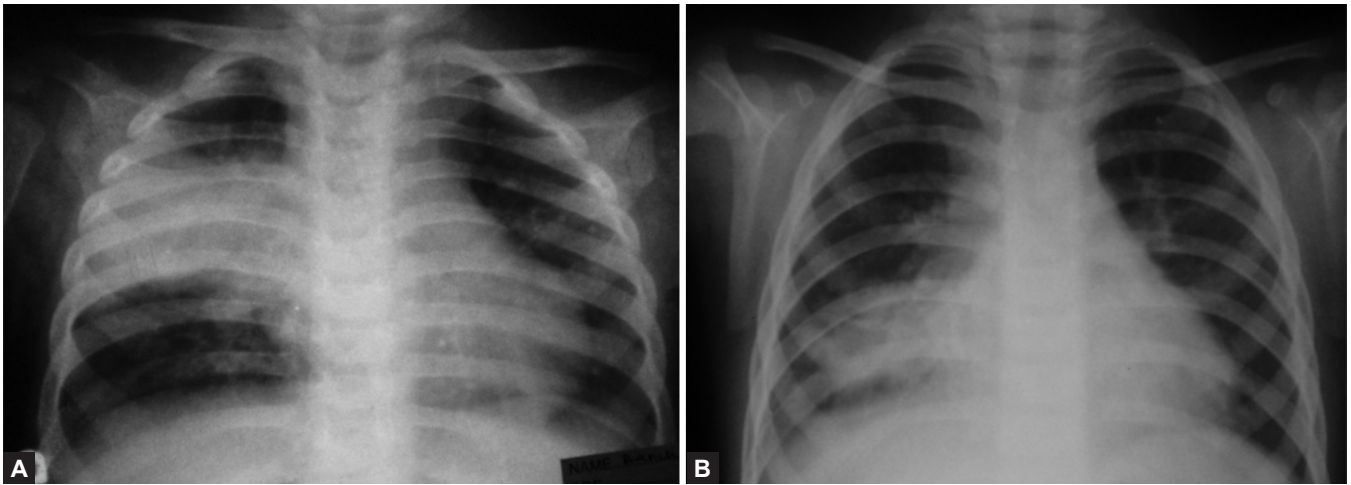
Oxygen saturation measurements through pulse oximetry provide a noninvasive estimate of arterial oxygenation and are useful for monitoring the severity of respiratory dysfunction, but have no role as an etiological test.

Imaging

Chest radiographs are less reliable in distinguishing viral from bacterial pneumonia and also do not reliably distinguish among the various possible bacterial pathogens. The usual patterns seen on a chest radiograph in a bacterial pneumonia are alveolar or airspace processes, and interstitial patterns usually reflect other etiologies; however an overlap is possible. A large lobar or diffuse consolidation (**Figs 2A and B**), a bulging fissure indicating extensive exudate or occult abscess in a lobar pneumonia, and associated pleural effusion are some findings highly suggestive of bacterial pneumonia. A diffuse, bilateral, fluffy infiltrate extending into the periphery suggests a bacterial process, central peribronchial infiltrate with or without atelectasis suggests a viral or *Mycoplasma* infection (**Fig. 3**). A peribronchial infiltrate with or without peripheral patchy alveolar opacification suggests a viral process (**Fig. 4**); a reticulonodular infiltrate confined to one lobe suggests *Mycoplasma pneumoniae*. Bronchopneumonia associated with lung necrosis, cavitation, pneumatoceles, and abscesses is more likely to be due to *S. aureus* (**Figs 5A and B**). Less commonly, *S. pneumoniae*, *H. influenzae*, and enteric gram-negative bacilli like *K. pneumoniae* and hydrocarbon aspiration can also result in necrotizing pneumonia.

Alveolar consolidative pneumonias can be further subclassified into two groups—airspace pneumonia and bronchopneumonia. Airspace pneumonia starts in the peripheral parenchyma and is acquired by the inhalation of small particles, e.g., pneumonia caused by *S. pneumoniae*, *Legionella*, and *K. pneumoniae*. Consolidation spreads concentrically because of the production of exudate and results in a spherical infiltrate (round pneumonia). Bronchopneumonia starts adjacent to centrally located bronchi and is acquired by the aspiration of infective particles.

Chest X-rays are not routinely necessary in patients being treated on OPD basis with a strong clinical suspicion of pneumonia. However, frontal views of chest radiographs should be performed in patients with suspected or documented hypoxemia or significant respiratory distress and in patients with failed initial antibiotic therapy to verify the presence or absence of complications of pneumonia, including pneumothorax, parapneumonic effusions and necrotizing pneumonia. Chest radiography for the diagnosis of pneumonia is not routinely recommended in patients with wheezing in the absence of fever or hypoxemia. It may however be obtained in those with severe disease requiring admission to document the presence, size, and character of parenchymal infiltrates and identify complications that may require other therapy. Lateral X-rays are not routinely required in pediatric age group and lead to unnecessary radiation exposure. Routine follow-



Figures 2A and B (A) Consolidation right superior basal segment; (B) Right middle lobe segmental pneumonia



Figure 3 Parahilar pneumonia caused by *Mycoplasma*

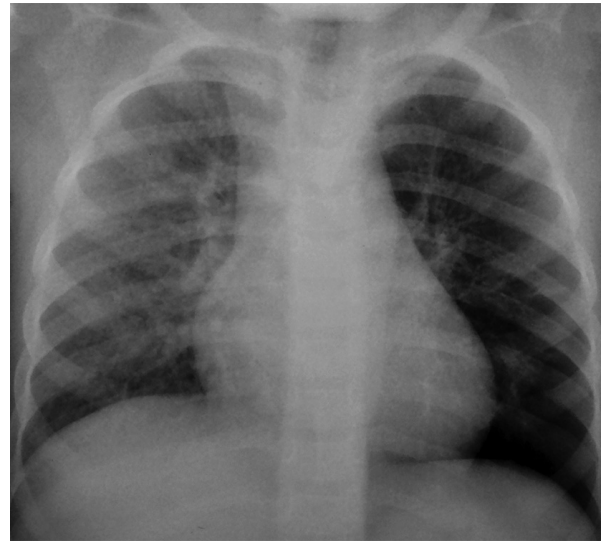
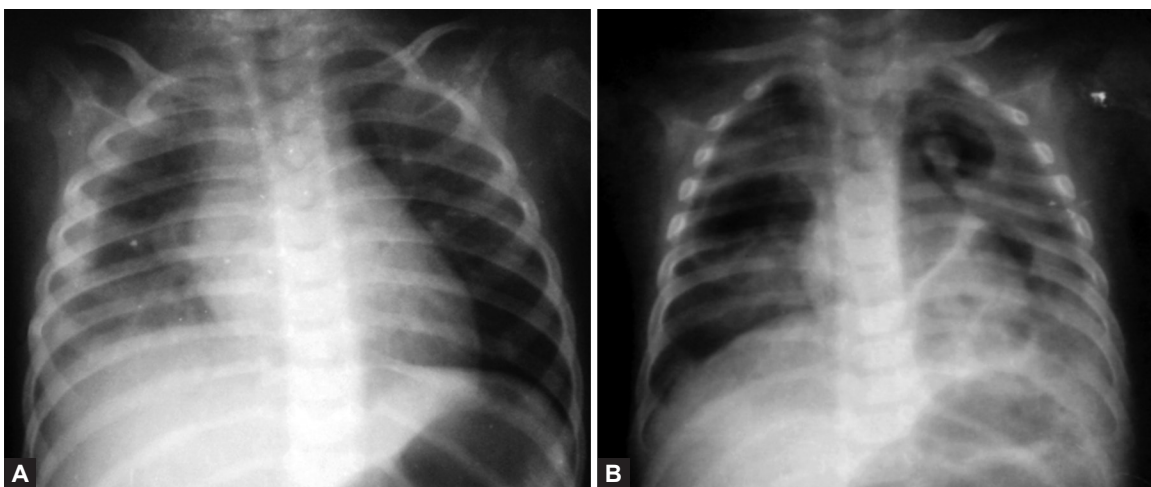


Figure 4 Interstitial pneumonia caused by viral infection



Figures 5A and B (A) Staphylococcal pneumonia complicated by right side pleural effusion with areas of breakdown; (B) Staphylococcal pneumonia complicated by multiple pneumatocele and left pleural effusion

up chest radiographs are not warranted in cases of uneventful recovery. Indications of repeat chest radiograph are:

- Failure to demonstrate clinical improvement
- Progressive symptoms or clinical deterioration within 48–72 hour after initiation of antibiotic therapy
- Complicated pneumonia with worsening respiratory distress or clinical instability
- Persistent fever that is not responding to therapy over 48–72 hours
- Recurrent pneumonia involving the same lobe
- Lobar collapse on initial chest radiography with suspicion of an anatomic anomaly, chest mass, or foreign body aspiration.

Ultrasonography of chest is an operator dependent modality which is now coming up as a bedside modality for intensive care unit settings. It is helpful in identifying early cavitation and in distinguishing a pneumonic process from avascular cavities and to identify fluid collections. CT chest, due to its high radiation, has no role in routine cases.

TREATMENT

An effort should be made to identify the possible etiologic agent based on the clinical and laboratory criteria so that the use of antibiotics can be minimized and the danger of antibiotic resistance curtailed (**Table 5**).

Table 5 Antimicrobial treatment as per suspected or documented etiology

<i>Disease</i>	<i>Pneumonia</i>		
<i>Setting</i>	Domiciliary		
<i>Age</i>	<i>First line</i>	<i>Second line</i>	<i>Suspected Staphylococcal disease</i>
Up to 3 months of age	Usually severe, treated as inpatients		
3 months to 5 years of age	Amoxycillin	Co-amoxyclav OR Cefuroxime	Amoxycillin + Cloxacillin (1:2) OR Cefuroxime OR Co-amoxyclav
Above 5 years of age	Amoxycillin	Co-amoxyclav OR Macrolide (atypical pneumonia)	Amoxycillin + Cloxacillin (1:2) OR Cefuroxime OR Co-amoxyclav
<i>Disease</i>	<i>Severe pneumonia</i>		
<i>Setting</i>	Inpatient		
<i>Age</i>	<i>First line</i>	<i>Second line</i>	<i>Suspected Staphylococcal disease</i>
up to 3 months	Inj 3rd generation Cephalosporins: Cefotaxime/ Ceftriaxone ± Aminoglycoside (Genta/amika)	Inj Co-amoxyclav (if suggestion of gram-positive disease) Else Inj Piperacillin-tazobactam or Cefoperazone-sulbactam (if suspecting resistant gram-negative disease)	Inj 3rd generation Cephalosporins: Cefotaxime/Ceftriaxone + Cloxacillin OR Inj Cefuroxime ± Aminoglycoside OR Inj Co-amoxyclav + Aminoglycoside Second line: Vancomycin/Telcoplanin + inj 3rd generation Cephalosporins
3 months to 5 years of age	Inj Ampicillin + Genta	Inj Co-amoxyclav OR Inj 3rd Generation Cephalosporins: Cefotaxime/ Ceftriaxone	Inj 3rd generation Cephalosporins: Cefotaxime/Ceftriaxone + Cloxacillin OR Inj Cefuroxime/Cefazolin OR Inj Co-amoxyclav Second line: Vancomycin/Telcoplanin + inj 3rd generation Cephalosporins
5 years plus	Inj Ampicillin	Inj Co-amoxyclav OR Inj 3rd Generation Cephalosporins: Cefotaxime/Ceftriaxone OR Macrolides	Inj 3rd generation Cephalosporins: Cefotaxime/Ceftriaxone + Cloxacillin OR Inj Cefuroxime/Cefazolin OR Inj Co-amoxyclav Second line: Vancomycin/Telcoplanin + Inj 3rd generation Cephalosporins

Outpatient Treatment

In previously healthy children with suspected bacterial pneumonia being treated on OPD basis, amoxicillin is the first-line antibiotic in a dose of 50 mg/kg/day, given in two or three divided doses. If epidemiology is suggestive of resistant pneumococci (currently this is not the status in India), higher doses (90 mg/kg/day) with 8 hourly dose intervals may be used. No oral cephalosporin at doses studied in children provides activity against resistant pneumococci at the site of infection that equals high-dose amoxicillin. *S. pneumoniae* and *H. influenzae* strains are often resistant to macrolides (about 35% of isolates in our country) and therefore, macrolides are not recommended as empiric therapy. In case of nonserious allergy to β -lactams, trial of amoxicillin or oral cephalosporin (cefuroxime or cefpodoxime) under medical supervision can be done. If there is history suggestive of serious allergy including anaphylaxis, other options like macrolide, fluoroquinolone or linezolid can be tried.

Cefixime is not recommended as a respiratory antibiotic as it has poorer action against *Pneumococcus* as compared to other second and third generation oral cephalosporins.

Role of Micronutrients and Vitamins

A randomized controlled trial (RCT) in pneumonia cases (age group 2 months to 5 years) showed no beneficial effect of short-term supplementation of vitamin D for resolution of severe pneumonia. Vitamin A and zinc supplementation also appear to have no role in either prophylaxis or management of childhood pneumonia.

Indications of Hospitalization (Table 6)

The children with severe pneumonia should be hospitalized for management. World Health Organization (WHO) defines *pneumonia* as cough or difficulty breathing plus one of the following: lower chest in-drawing, nasal flaring, or grunting. Severe pneumonia is defined as *cough or difficulty breathing plus one of the following: cyanosis, severe respiratory distress, inability to drink or vomiting everything, or lethargy/unconsciousness/convulsions*. Infants less than 3 months have nonspecific signs and often can have associated sepsis/meningitis and are therefore almost always be hospitalized and treated as severe disease with a combination therapy.

Inpatient Supportive Therapy

Patients whose oxygen saturation is less than 92% while breathing air should be treated with oxygen given by nasal cannulae, high-flow delivery device, head box or face mask to maintain oxygen saturation more than 92%. Nasogastric tubes may compromise breathing and should therefore be avoided in severely ill children. Where needed, using orogastric tubes for feeding may be preferred to avoid blocking a nostril. Intravenous fluids should be used judiciously and serum electrolytes monitored. Antipyretics should be used to control fever and it helps in decreasing the oxygen demand in such cases.

Inpatient Antibiotic Therapy

Children with severe and life-threatening bacterial pneumonia should be started on parenteral antibiotics to achieve optimal

blood and tissue concentrations. Around 1% of children with pneumococcal pneumonia may have meningitis as well; therefore, the antibiotics are required in higher doses. The empiric antimicrobials being recommended are for the bacterial pathogens most likely to cause pneumonia, especially *S. pneumoniae*. Routine use of antibiotics is not indicated in preschoolers as many cases of pneumonia are due to a viral etiology. Clinical decision, as discussed earlier, and good follow-up in such cases can be useful in rationalizing antibiotic usage.

Infants and school-aged children with severe pneumonia requiring admission should be started on injection ampicillin or penicillin G. If penicillin resistance in *S. pneumoniae* is suspected or in infants and children with life-threatening infection where *H. influenzae b* could be the offending organism, patients should be started on parenteral third generation cephalosporins (cefotaxime or ceftriaxone). Intravenous co-amoxycyclavulanate is as effective as third generation cephalosporin. A macrolide can be added to a β -lactam antibiotic in children whom *M. pneumoniae* or *C. pneumoniae* is suspected.

If there is a suspicion of infection due to *S. aureus*, cloxacillin can be added to the β -lactam therapy or else co-amoxycyclavulanate can be used. In failure or resistant cases, vancomycin or clindamycin can be added to the β -lactam therapy.

Duration of Treatment

Total course of therapy depends on severity, rapidity of response and the likely organism. Most community acquired pneumonia will need treatment for 5 days while severe admitted cases shall need 7–10 days of therapy. In the presence of complications or infection with *S. aureus*, duration of therapy might be prolonged to 4–6 weeks. In the absence of bacteremia, or in children with bacteremia in whom secondary foci of infection have not been found, transition to oral therapy can take place as soon as the patient is stable and able to take orally, which may be as early as 2–3 days after the start of parenteral therapy.

Response to Therapy

Children receiving adequate therapy should demonstrate clinical and laboratory signs of improvement within 48–72 hours. It must be ensured that the correct drug(s) and dosages were prescribed and there was adherence to therapy. If there is no response to adequate medical management, further investigations may need to be carried out to look for any evidence of complications or presence of resistant pathogens. However, in case of complicated pneumonia, particularly with staphylococcal disease, the response is usually slower and can take up to 4–6 days and may not require any investigation unless a complication is suspected due emergence of new signs or symptoms.

Criteria for terming nonresponse to treatment at 48–72 hours are as follows:

- *Vital signs and parameters*
 - Persistence or increase in the general fever pattern
 - Increased respiratory rate, grunting, chest retractions, cyanosis

Table 6 Indications for hospitalization in children with pneumonia

1.	Moderate to severe pneumonia defined by respiratory distress (tachypnea > 70/min, retractions, grunting, nasal flaring or head bobbing) and hypoxemia ($SpO_2 < 90\%$)
2.	Children less than 6 months of age with suspected bacterial pneumonia
3.	Dehydration, vomiting or inability to take oral medication
4.	Presence of comorbid conditions, e.g., immunologic disorders, hematologic, cardiac, and chronic pulmonary conditions, genetic syndromes, neurocognitive disorders, reactive airway disease
5.	Children or infants with concerns regarding compliance with proper therapy or follow-up

- Persisting or increased heart rate
- Oxygen saturation less than 90% with room air, need for supplemental oxygen or ventilation
- *Systemic or focal symptoms or signs*
 - Clinically defined *toxicity* based on clinical judgment or change in mental status
 - Chest pain, splinting of the chest
 - Inability to maintain oral intake and hydration
 - Change in the extent of abnormal or absent breath sounds at auscultation or dullness in response to percussion
- Laboratory and/or radiologic results
 - Raised WBC count, both total count and percentage of immature forms of neutrophils
 - Increasing levels of inflammatory markers (e.g., procalcitonin, CRP)
 - Isolation of a pathogen by culture; nonresponsive pathogens include either those with antimicrobial resistance to current therapy or those susceptible to current therapy but with inadequate drug exposure in infected tissues, inadequate drainage of empyema or abscess, or inadequate duration of therapy
 - Increased parenchymal involvement, presence of or increase in pleural fluid, or development of pulmonary abscess or necrotizing pneumonia as documented on imaging.

Apart from drug resistant infection, other important reasons to be kept in mind in case of nonresponse are suspicion of tuberculosis, human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS), or presence of severe malnutrition.

CRITERIA FOR DISCHARGE

- Improvement in general condition, activity and appetite and stable or baseline mental status,
- Pulse oximetry more than 90% at room air for at least 12–24 hours,
- No evidence of increased work of breathing in the form of tachypnea, tachycardia, retractions and nasal flare,
- Patients are able to tolerate oral medications and feeds,
- No social issues regarding observation at home, compliance to therapy or regular follow-up by parents/caregivers.

PREVENTION

Primary Prevention

Key primary measures to reduce deaths due to ARI include promoting adequate nutrition, increasing immunization coverage rate, reducing indoor air pollution and imparting health education. Preventing childhood pneumonia is critical to millennium developmental goal-4 target of reducing child deaths.

Promotion of exclusive breastfeeding till 6 months of age, and appropriate initiation of complementary feeds can reduce mortality due to ARI. Similarly, improving maternal nutrition status and micronutrient (vitamin/mineral) supplementation reduces the risk of low birthweight infants which in turn improves the overall survival associated with ARI in infants and children.

Immunization Effective implementation of expanded program on immunization (EPI) would in turn strengthen the ARI control program. Vaccines against diphtheria, pertussis and measles when given appropriate coverage can drastically decrease the mortality associated with ARI. Vaccination against *Pneumococcus*, and *H. influenzae* type B may decrease the incidence and deaths associated with pneumonia in children.

Health education about ARI begins from parents who need to learn to recognize severe forms, understand when to take their child to health-care center and make use of appropriate health-care

facilities. They need to be sensitized for promotion of breastfeeding, cessation of parental smoking and reducing indoor air pollution. It needs to be extended to primary health-care (PHC) worker to identify which children require home care, and which cases need to be referred. Education needs to be imparted to hospital/first referral unit (FRU) staff to manage complicated cases.

Secondary Prevention

Early diagnosis and treatment with antibiotics can prevent large proportion of deaths due to ARI. Case management of ARI essentially consists of

- Differentiation or identification of clinical condition by degree of severity,
- Initiation of appropriate antibiotics,
- Timely and appropriate referral monitoring and follow-up.

ACUTE RESPIRATORY INFECTION CONTROL PROGRAM

Acute respiratory infection control program was initiated officially by WHO in the year 1978 with the main objective of reducing the mortality from childhood pneumonia. It was recommended that by 1989 most of the developing countries should have formulated national programs for control of ARI within PHC. ARI control program was started by government of India in 1990 as a pilot project in four districts. Ten new districts were added in the year 1991. It sought to introduce scientific protocols for case management with rational and judicious use of antibiotics.

The main objective of ARI program is to reduce high mortality from ARI in children under-5 years through health education, effective case management and immunization against diphtheria/pertussis/measles which contribute substantially to overall ARI morbidity and mortality. Since 1992 the program was implemented as a part of Child Survival and Safe Motherhood (CSSM) program of Government of India. By the year 1997, ARI control activities were integrated with Reproductive and Child Health (RCH) program where efforts to improve ARI control program and effective management of infection were the focus of child health services at PHC. Generation of technical guidelines (WHO-ARI treatment guidelines) is simple classification for use by community health workers. ARI has been covered under the integrated management of childhood and neonatal illness (IMNCI). Based on selected clinical signs the child is placed in a classification and treated accordingly (see Chapter 51.5).

GLOBAL ACTION PLAN FOR PNEUMONIA

Global action plan for pneumonia (GAPP) was proposed by WHO following a meeting of experts on 5th–7th March, 2007 at France. The objectives of the plan include:

1. To identify topics for review in developing technical consensus on interventions to be promoted and strategies for accelerating their use in developing countries.
2. Develop outlines for each review and identify groups to develop the reviews.
3. Reach consensus on the process and timelines for development of GAPP.

GAPP was proposed to increase the awareness of pneumonia as a major cause of death, to scale up the use of interventions of proven benefit and to develop a plan to achieve this. Key strategies for control of pneumonia include effective case management at community and at health facility, achieve global immunization vision and strategy, improvement of nutrition and low birthweight, reduction in indoor air pollution, prevention and management of HIV infection.

IN A NUTSHELL

1. Pneumonia may be classified as simple and complicated pneumonia. Simple pneumonia can be bronchopneumonia and lobar pneumonia. Complicated pneumonia refers to effusions, empyema, necrotizing pneumonia abscesses or cavities, pneumothorax or bronchopleural fistula.
2. Viruses are among the frequent pathogens in children younger than 2 years. RSV is most commonly implicated virus.
3. Among the bacterial causes of pneumonia in young children, *Streptococcus pneumoniae* and *Haemophilus influenzae* are the most common.
4. Malnutrition, low birthweight, and lack of exclusive breastfeeding, predispose to pneumonia. Maternal education and awareness influence the care seeking behavior for children with pneumonia.
5. Tachypnea is a simple yet fairly specific and sensitive sign for pneumonia if asthma and bronchiolitis have been excluded.
6. Children with pneumonia usually present with fever, tachypnea, productive cough, and chest pain. In pneumonia caused by atypical pathogens, a more gradual onset associated with low grade fever or no fever, headache, nonproductive cough and malaise may be present.
7. Chest X-rays are not routinely necessary in patients being treated on OPD basis with a strong clinical suspicion of pneumonia.
8. In previously healthy children with suspected bacterial pneumonia being treated on OPD basis, amoxicillin is the first-line antibiotic in a dose of 50 mg/kg/day, given in two or three divided doses.
9. Children with severe or very severe pneumonia (as per WHO definitions) should be hospitalized for management.
10. Children with severe and life-threatening bacterial pneumonia should be started on parenteral antibiotics and offered supportive therapy.

MORE ON THIS TOPIC

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Chapter 39.22

Parapneumonic Effusion and Empyema

Kamal Kumar Singhal, GR Sethi

Empyema is defined as pus within the pleural space. Usually a complication of bacterial pneumonia, it can occasionally occur as a consequence of infection at other sites. Recent reports indicate that the incidence is increasing worldwide. The condition rarely resolves without medical therapy, which includes antibiotics and chest tube drainage. Other forms of treatment include use of fibrinolytics, video-assisted thoracoscopic surgery (VATS), open thoracotomy and decortication.

EPIDEMIOLOGY

Parapneumonic effusion and empyema have an incidence of 3.3 per 100,000 children and occur in 0.7% of children with pneumonia. The mean age of affected children is between 4 years and 6 years. Historically, the rate of empyema in pneumonia has shown much fluctuation. The preantibiotic era rate of about 10% diminished greatly in the antibiotic era and then again surged in the middle of the 20th century to about 14% to decrease in 1970s to about 2%. Many recent reports have again indicated an increase in worldwide incidence of empyema. The reasons for this rise are not clearly understood.

Pleural infection is most commonly a complication of bacterial pneumonia. Thus patients at risk for pneumonia are also at risk of pleural infection. Causes of pleural infection other than pneumonia, are largely iatrogenic, including thoracic (20%) and esophageal surgery, esophageal perforation, and trauma (5%). Empyema may occur due to thoracocentesis, intervention for primary spontaneous pneumothorax and abdominal sepsis or spontaneous bacterial peritonitis in 2%, 2% and 1% cases, respectively. Rarely, a primary infection of the pleural space may occur. Cause in up to one-third of cases is idiopathic.

ETIOLOGY

The most common organisms that cause effusions or empyemas associated with community-acquired pneumonia (CAP) in children are *Streptococcus pneumoniae* and *Staphylococcus aureus*. Pneumococcal infection is the most common cause in developed countries and *S. aureus* in the developing world. In one of the studies, anaerobic bacteria were isolated in 13%, and mixed aerobic and anaerobic bacteria in 23% patients, indicating a greater role of anaerobes in empyema. There is marked variability in the reported microbiology of empyema depending on the reported series and clinical settings. Resistant organisms (particularly methicillin-resistant *Staphylococcus aureus* [MRSA]) are a common cause of hospital-acquired pleural infection. Empyema secondary to external introduction of organisms, e.g., trauma, surgery, thoracocentesis is more likely due to *S. aureus* or aerobic gram-negative bacilli. Empyema secondary to subdiaphragmatic abscess may be due to mixed organisms and may include enteric gram-negative bacilli, other aerobic intestinal flora, or anaerobes.

PATHOGENESIS

The pleura is a serous membrane divided into parietal and visceral pleura. The visceral pleura covers the lung parenchyma while the parietal pleura covers the diaphragm, mediastinum and rib

cage. Pleura allows for mechanical coupling of the lung and chest wall throughout the respiratory cycle. Approximately 0.3 mL/kg of fluid is normally present in the pleural space and it lubricates the movement of visceral pleura on the parietal pleura during respiration. This pleural fluid is the result of a dynamic balance between fluid filtered from subpleural capillaries and removed via lymphatics. Between the mesothelial cells of the mediastinal and intercostals aspect of costal pleura, 2–12 μm openings called *stomata* are present. It is through these stomas that the lymphatic vessels communicate with the pleural space. Pleural fluid accumulates if there is an imbalance in its formation and absorption.

Transudate versus Exudate

Pleural effusion can be either a *transudate* or *exudate*. Transudative effusion are due to altered systemic factors influencing the formation and absorption of pleural fluid (e.g., cardiac failure, nephrotic syndrome), whereas exudative effusions are due to altered pleural surface or capillaries (e.g., infections). Exudative effusion meets at least one of the following criteria given by Light: pleural fluid protein divided by serum protein greater than 0.5, pleural fluid lactate dehydrogenase (LDH) divided by serum LDH greater than 0.6, and pleural fluid LDH greater than two-thirds of upper limit of normal for serum LDH. Since light criteria was developed and tested in adults, its applicability in children has been questioned.

Evolution of Empyema

Although the progression of pleural fluid associated with infections to empyema is a continuum: it has been classically divided into three stages—(1) exudative, (2) fibrinopurulent and (3) organizing.

Exudative Stage

In this stage the inflammatory process associated with the underlying pneumonia leads to the accumulation of clear fluid with a low white cell count within the pleural cavity (simple parapneumonic effusion). It usually lasts 3–5 days.

Fibrinopurulent Stage

Usually starts 7–10 days after the first signs of the acute disease. In this stage there is bacterial invasion across the damaged epithelium and accumulation of fibrinous strands in the pleural fluid leading to septations and loculations. Further there is an increase in white cells, with the fluid thickening (complicated parapneumonic effusion) and eventually becoming overt pus (empyema). All empyemas are complicated effusions but not *vice versa*. This combination of events leads to increased lactic acid production, associated with a fall in pleural fluid pH, accompanied by increased glucose metabolism and a rise in LDH levels due to leukocytes death.

Organizing Stage

This stage involves proliferation of fibroblasts and starts in 2–3 weeks. Due to these fibroblasts a solid, thick, fibrous pleural peel replaces the soft fibrinous membrane. This nonelastic pleural peel prevents the re-expansion of lung and impairs lung function, creating a persistent pleural space with continuing potential for infection.

CLINICAL FEATURES

The clinical presentation of empyema may be acute or chronic. The acute presentations of empyema are of two types. The first type clinically resembles acute pneumonia and presents with cough, fever, tachypnea, respiratory distress, exercise intolerance,

poor appetite, abdominal pain, lethargy and malaise. However, compared to simple pneumonia these children are often more unwell and have pleuritic chest pain. The second type, and the more common one, resembles a worsening or nonresponding pneumonia. These patients present with persistence of fever, and respiratory symptoms in a child with of pneumonia or feature of relapse in a resolving pneumonia. Chronic empyema may have only nonspecific constitutional symptoms like weight loss and low grade fever without any local chest symptoms. Very young children with empyema may present with predominantly abdominal signs and symptoms. They may have pain abdomen and even abdominal distension.

On inspection pleural effusion may be suggested by unilateral signs of bulging of the intercostal spaces, decreased chest expansion, splinting of chest, preference to lie with normal side up and affected side in dependent position, focal chest wall heat, erythema, swelling and scoliosis. On palpation the trachea and cardiac impulse may be shifted away from the side of effusion with decreased tactile fremitus, and chest wall expansion on affected side. The affected side may be stony dull on percussion. Auscultation will reveal decreased breath sound on affected side. There may be pleural friction rub, bronchophony or egophony above pleural effusion. This paradoxical increase of breath sounds near the upper border of the fluid is due to increased sound conductance in the partly atelectatic area under the fluid.

Complications of empyema include bronchopleural fistula (communication between bronchial airway and pleural space), empyema necessitans (extension of pus out of the pleura into the chest wall and surrounding soft tissue) and pneumothorax. Infective complications include pericarditis and bacteremia.

DIAGNOSIS

Acute Phase Reactants

These cannot differentiate simple pneumonia from complicated pneumonia with empyema, or empyema from simple parapneumonic effusion.

Blood Culture

Recommended in all cases for identification of the organism, although yield is low (10–22%).

Pleural Fluid Cytology, Biochemistry and Culture

This should be aimed in all cases. Thoracentesis is required for differentiation of uninfected parapneumonic effusion from empyema. Pleural fluid thus obtained should be sent for cytology, Gram stain, microbiological and biochemical investigations, culture. The following characteristics of pleural fluid strongly suggest presence of empyema; thick pus, bacteria on Gram stain, glucose level less than 60 mg/dL or pleural fluid to serum glucose ratio of less than 0.5, LDH levels of more than 1,000 IU/L, and pH below 7.3.

Chest X-ray

On erect frontal view small pleural fluid is seen as obliteration of the costophrenic angle and larger fluid as meniscus sign (a rim of fluid ascending the lateral chest wall). In supine position, pleural fluid is seen as homogeneous increase in opacity over the whole lung field. Big pleural effusions are seen as complete white-out of one lung field (**Fig. 1**). Scoliosis with concavity to the side of the effusion may also be seen in chronic cases.

Three features described here may distinguish simple parapneumonic effusion from empyema on chest X-ray. Firstly, shift of pleural fluid location with change in position of patient (erect to lateral decubitus or *vice versa*) indicates simple parapneumonic effusions. Presence of loculations in empyema

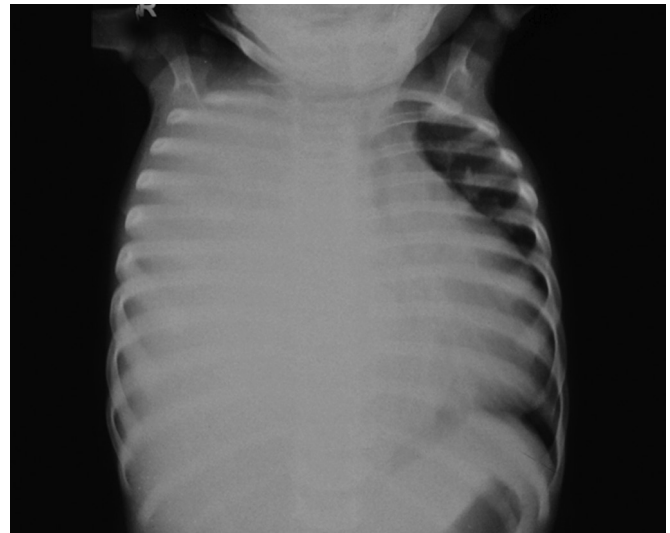


Figure 1 Right-sided pleural effusion seen as complete white-out of one lung field

hinders this free shift of fluid location. Secondly, presence of lung abscess or cavitary pneumonia or an adjacent pulmonary alveolar consolidation favors presence of empyema. Thirdly, pleural collection having a lenticular shape with internal convexity may indicate loculations because a freely moving collection should form an internally concave meniscus paralleling the chest wall.

On chest X-ray pulmonary abscess and empyema can be differentiated by obtaining two X-ray views perpendicular to each other, usually lateral and frontal projections. The length of air-fluid level is equal in case of abscess and unequal in case of empyemas.

Although useful for diagnosis of empyema in a patient showing inadequate resolution or worsening of pneumonia, chest X-ray is not useful for follow-up, since radiological resolution takes time. Almost 80% chest X-ray shows resolution at 3 months and almost all by 1½ year.

Ultrasonography

Typically, pleural effusions on ultrasonography can be classified into three groups: (1) anechoic, (2) complex nonseptated, and (3) septated. The anechoic and complex nonseptated patterns can be seen in both transudates and exudates. The septated pattern can be seen only in exudates. Moreover the term *septated* is not the same as *loculated*. While loculated collections do not communicate, septated ones simply mean presence of fibrinous strands within the pleural fluid.

Ultrasonography is a better modality than computed tomography (CT) scan to assess for fibrinous septations in the pleural fluid and to differentiate free from loculated fluid. It can be conveniently used bedside to mark the best site for insertion of intercostals drainage tube. It can also give a good estimate of the amount of pleural fluid. In cases of white-out lung, due its good ability to distinguish solid from liquid structures, it can be used to differentiate between atelectasis, consolidation, and effusion. Ultrasonography can readily distinguish pleural fluid from pleural thickening.

CT Scan

Computed tomography (CT) scan allows complete examination of the thorax. Although unnecessary for most cases of pediatric empyemas, it is indicated in complicated cases or when an alternative diagnosis is suspected, e.g., tumor or abscess. Performed before thoracotomy or thoracoscopy, it gives greater

anatomic details to a surgeon. It is the best method to differentiate a peripheral lung abscess from empyema. Abscesses have an irregular thick wall which is not uniformly wide and do not have a discrete boundary between the lesion and lung parenchyma. In contrast, empyemas have a regularly shaped lumen, a smooth inner surface, and a sharply defined border between the lesion and lung. Since CT cannot visualize fibrin strands or loculations, as they are too thin, it cannot differentiate simple parapneumonic effusion from empyema.

MANAGEMENT

The general care of the patient would include judicious use of oxygen, antipyretics, intravenous (IV) fluids, and IV antimicrobial. Pus drainage and appropriate antibiotic therapy is the mainstay of all therapeutic options.

Treatment goals in empyema include sterilizing the pleural cavity with antibiotics (preferably IV), with drainage of fluid, re-expansion of the lung, and restoration of normal lung function. The treatment approach should be based on clinical status, radiological staging and the results of pleural fluid examination. It is important to document the stage of pleural effusion (exudative, fibropurulent or organizational stage) before selecting the most appropriate intervention.

Currently available treatment options for pediatric parapneumonic effusion and empyema include antibiotics alone or antibiotics with thoracentesis, chest tube drainage (alone or in combination with fibrinolytics), and surgery (VATS or open thoracotomy with decortication).

Antibiotic Therapy

Small stable pleural collections can be managed with antibiotics alone. Antibiotic treatment is empiric since the majority of patients do not have any positive culture results. Generally, IV broad-spectrum high dose antibiotics (amoxycillin with clavulanic acid, cloxacillin with gentamicin, or cloxacillin with ceftriaxone) are started. If MRSA is suspected then one prefers vancomycin. In suspected hospital-acquired infection or in patients with a prior transthoracic procedure a combination of carbapenems (e.g., meropenem) and a drug with anti-MRSA activity (e.g., vancomycin) may be needed. The antibiotics may need to be changed with the availability of culture sensitivity pattern. The recommended duration is for 2–4 weeks after discharge (which is usually after 2 weeks of IV treatment) or even longer when there is residual disease.

Chest Tube Drainage

Enlarging exudative collections would need drainage in addition to antibiotics. This requires intercostals chest tube placement. Repeated ultrasonography guided needle thoracentesis causes repeated trauma, and has not been found to be more effective than chest tube placement. If there is inadequate clinical response (fever spikes, rising total leukocyte counts [TLC], poor oral intake) despite antibiotic cover and adequate intercostal drainage, there may be a need for review antibiotics. If pleural fluid drainage is inadequate, it may merit adjustment of existing chest tube or insertion of another chest tube, or consideration of fibrinolytic therapy or surgery. A CT scan is required only in such patients.

If there are loculations on imaging, intrapleural fibrinolytic therapy may be considered, but benefit from use of fibrinolytics in empyema is inconsistent across various studies. Evidence is still not sufficient to recommend routine use.

Surgical Options

Surgery is indicated in cases with failure of medical therapy (persisting sepsis and large pleural collection), chronic empyema, and persistent bronchopleural fistula. Surgical modalities in use include: (i) video-assisted thoracoscopic surgery (VATS); and (ii) open thoracotomy.

Studies reporting conservative management (antibiotics and chest tube drainage) in children are few, mostly from west. And now with new management strategies such studies have become even less common. Further availability of local resources and cost limits the surgical option, especially in developing countries. Studies comparing intercostal chest drain and urokinase with VATS for the treatment of empyema in children did not find any difference in clinical outcome but cost of treatment was significantly lower in the urokinase group. Nonetheless, VATS or thoracotomy may be considered in complicated empyema, where it is available. The success rate with thoracoscopy and thoracotomy is 60–90% respectively. Thoracotomy with decortication remains the initial treatment of choice in all chronic and multiloculated empyemas.

What is of utmost importance is the fact that the primary goal of all initial interventions is the control of the pleural infection. If it is controlled then pleural adhesions on imaging or abnormal lung functions do not merit any immediate surgical procedure. These patients can be conservatively observed since a number of studies have reported that children with empyema almost always recover, irrespective of the treatment they receive.

IN A NUTSHELL

1. Empyema is mostly a complication of bacterial pneumonia.
2. *Streptococcus pneumoniae* and *Staphylococcus aureus* are the most common causative pathogens.
3. Very young children may present with predominantly abdominal signs and symptoms.
4. Ultrasonography is a better modality than CT scan to differentiate free from loculated fluid.
5. Thoracentesis is ultimately required for differentiation of uninfected parapneumonic effusion from empyema.
6. Appropriate antibiotic therapy (for 4–6 weeks) with chest tube drainage is the mainstay of therapy.

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Chapter 39.23

Pneumothorax and Air Leaks

Mandeep Walia, Abhishek Somasekhara Aradhya

Air leaks are now increasingly encountered in pediatric patients, with increased use of assisted ventilation. Accumulation of air in the intrapleural space is defined as pneumothorax and is the most common air leak syndrome in children, followed by pulmonary interstitial emphysema. The other causes of air leak include pneumomediastinum, pneumopericardium, pneumoperitoneum, and subcutaneous emphysema. In many patients air leaks may present as a life-threatening event warranting prompt recognition and expedited drainage.

PNEUMOTHORAX

By convention, a small pneumothorax occupies less than 15% of lung volume, while moderate and large pneumothorax occupies 15–60% and more than 60%, respectively.

ETIOLOGY

Pneumothorax can be classified as spontaneous, iatrogenic, traumatic or catamenial. Based on intrapleural air pressure, it can be simple or tension pneumothorax. Spontaneous pneumothorax is further classified as primary or secondary. Primary spontaneous pneumothorax involves no underlying lung disease or trauma. Pneumothorax occurring due to an underlying lung disease, but without trauma is defined as secondary spontaneous pneumothorax.

Primary Spontaneous Pneumothorax

Primary spontaneous pneumothorax occurs more commonly in tall, thin males with marfanoid habitus. In these children, periods of active growth are accompanied by an increase in the vertical dimensions of the chest that may affect intrathoracic pressure at the apices and drive subpleural cyst formation. Other genetic conditions which pose a risk factor for primary spontaneous pneumothorax include Ehlers-Danlos syndrome, homocystinuria, Birt-Hogg-Dube syndrome and rheumatological conditions like ankylosing spondylitis. Birt-Hogg-Dube syndrome is a rare autosomal dominant condition with folliculin gene mutation with benign skin tumors, renal and gastrointestinal malignancies, with thin wall cysts in the lung which can rupture to cause pneumothorax in one-fifth of the cases. Spontaneous pneumothorax can also be seen with substance abuse (heroin addiction).

Conventionally primary pneumothorax is defined to occur in the absence of lung disease; however a majority of them have been detected to have subpleural blebs and localized emphysematous changes on computed tomography (CT) of the chest. With the availability of novel techniques like fluorescein-enhanced autofluorescence thoracoscopy (FEAT), increased lung porosity has been identified in primary pneumothorax. Leakage from these porous sites leads to intrapleural accumulation of air.

Secondary Pneumothorax

Secondary pneumothorax occurs in presence of underlying lung disease. In a tropical country like India, necrotizing pneumonia, especially due to *Staphylococcus aureus* is one of the most common

inciting causes. Pulmonary tuberculosis is also associated with secondary pneumothorax, due to rupture of pleural adhesions allowing air leak into pleural space. Other causes include, but not limited to lung abscess, cystic fibrosis, asthma, interstitial lung disease, *Pneumocystis jirovecii* pneumonia, histiocytosis, sarcoidosis, lung infarct, congenital malformations like cystic adenomatoid malformation, lobar emphysema, and rare tumors (**Table 1**). Children are more predisposed to pneumothorax than adults following trauma, even in the absence of external injury or rib fracture, due to greater distensibility of the chest wall. The incidence of iatrogenic pneumothorax has considerably increased with assisted ventilation (due to barotrauma) and other procedures like thoracentesis, tracheostomy, subclavian venous lines and transbronchial lung biopsy.

Neonatal Pneumothorax

Newborns have a higher incidence of pneumothorax approximately 0.5–3%, however, only 10% of these are symptomatic. Their increased predisposition is due to greater compliance and uneven alveolar distension owing to poorly developed pores of Kohn, which allows interalveolar air distribution. Aspiration syndromes, respiratory distress syndrome and sepsis are important risk factors for air leak. Air leaks in the newborn infants have been discussed in detail in Section 17.

Table 1 Causes of secondary pneumothorax in children

Primary spontaneous	Idiopathic
Secondary spontaneous	
Infection	Necrotizing pneumonia Measles Tuberculosis <i>Pneumocystis jirovecii</i> Echinococcal HIV
Increased intrathoracic pressure	Asthma Bronchiolitis Cystic fibrosis Airway foreign body
Congenital lung/airway anomalies	Congenital cystic adenomatoid malformation Bronchogenic cyst Congenital lobar emphysema
Inflammatory/connective tissue disorders	Marfan syndrome Ehlers-Danlos syndrome SLE Langerhans cell histiocytosis Dermatomyositis Polymyositis Sarcoidosis
Malignancy	Lymphoma Metastatic lung lesions
Traumatic	Blunt trauma Penetrating lung injury
Iatrogenic	Mechanical ventilation Thoracotomy Thoracentesis Thoracoscopy Tracheostomy Needle aspiration
Catamenial	

Abbreviations: HIV, human immunodeficiency virus; SLE, systemic lupus erythematosus.

Catamenial Pneumothorax

Catamenial pneumothorax is an unusual variety of recurrent pneumothorax predictably occurring during menstruation. It occurs due to transperitoneal migration of pelvic endometriosis through pores in right diaphragm. This entity is rare in adolescent girls.

PATHOPHYSIOLOGY

Pneumothorax occurs whenever there is uneven alveolar ventilation, air trapping and high transpulmonary pressure swings. The lung normally has an intrinsic property to collapse inwards. In the presence of intrapleural air there is uncoupling of the lung from the chest wall leading to further collapse, until equilibrium is achieved leading to alveolar hypoventilation and ventilation-perfusion mismatch thereby leading to hypoxia and hypercarbia.

In *tension pneumothorax*, pressure in the pleural space remains positive throughout the respiratory cycle due to a check valve leading to collapse of the ipsilateral lung. The contralateral lung is overinflated, further increasing the intrathoracic pressure. Consequently venous return is decreased, leading to poor peripheral perfusion. Compensatory tachycardia occurs which further restricts the stroke volume. Kinking of the inferior vena cava is thought to be the initial event in tension pneumothorax decreasing the preload to heart. The end result is cardiac arrest with electromechanical dissociation on electrocardiography.

CLINICAL FEATURES

Clinical presentation of pneumothorax mainly depends on age, rapidity of air accumulation, intrapleural pressure and consequent lung collapse. Symptom spectrum may range from asymptomatic accumulation of air in the pleural space to sudden cardiorespiratory collapse in tension pneumothorax. In asymptomatic children, diagnosis is first evident on a chest radiograph.

Primary spontaneous pneumothorax usually presents with pleuritic chest pain, although explanation for increased frequency of chest pain is not available. In contrast, breathlessness is the predominant presenting symptom in secondary pneumothorax, presumably due to an underlying reduced lung reserve and further lung collapse due to pneumothorax resulting in dyspnea.

Older children usually present with acute chest pain, breathlessness and cyanosis. On examination they have tachycardia, tachypnea, shallow breathing, hyperinflated chest on the ipsilateral side, shift of trachea to opposite side (late sign) with hyper-resonant note on percussion, absent breath sounds and decreased vocal resonance on same side. Tension pneumothorax additionally has features of mediastinal shift, jugular venous dilation, pulsus paradoxus, and cardiorespiratory compromise.

Children with spontaneous pneumothorax may be asymptomatic and are usually tall and thin adolescents with or without marfanoid habitus. Up to 10% of spontaneous pneumothorax has positive family history. Usually spontaneous pneumothorax present late as symptoms improve usually over 1–3 days.

Children on assisted ventilation and neonates usually present with tachycardia, tachypnea, irritability and chest bulge. Pneumothorax should be ruled out in any mechanically ventilated child developing sudden and unexplained alterations in hemodynamic or respiratory parameters.

DIAGNOSIS

Diagnosis of pneumothorax is suspected on clinical history and examination, confirmed on an erect chest radiograph in older children (**Fig. 1**). Contrary to adults, children often do not have peripheral lucency in supine films as gas collects anteriorly in anterior pleural reflection. Increased clarity of cardiac outline may

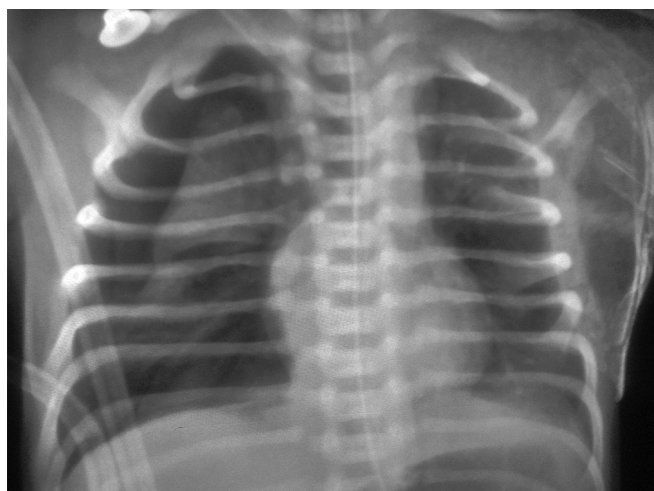


Figure 1 Right-sided pneumothorax

be the only finding in supine radiographs. Small pneumothorax not detected on posterioranterior view, may be revealed on a lateral or lateral decubitus views.

Radiographic findings of pneumothorax on an erect film include a thin white line of visceral pleura, usually seen in the apex of the lung, absence of lung markings beyond this white pleural line. Evidence of tension pneumothorax includes shift of the mediastinal structures to the contralateral side, flattening of the ipsilateral diaphragm. If tension pneumothorax is detected clinically, waiting for confirmation on a chest X-ray will waste crucial time. Air should be evacuated immediately.

Estimation of the size of pneumothorax has been described by several methods, including the Light, Rhea and Collin methods. However, their accuracy in child patients has not been assessed. British Thoracic Society guidelines for adult patients defines a large pneumothorax as more than or equal to 2 cm space between the lateral lung edge and chest wall and this approximates to a pneumothorax size of 50%.

Cystic lung lesions and lobar emphysema may mimic a pneumothorax on chest radiograph. Both these entities however have crescentic lower border of radiolucency. To differentiate diaphragmatic hernia, pass a nasogastric tube. The radiopaque tip of the tube, when visualized in the thoracic cavity indicates a diaphragmatic hernia, which can be confirmed on ultrasonography.

MANAGEMENT

The decision to treat pneumothorax depends on its extent, symptomatology of the patient and underlying lung reserve. Small pneumothorax (less than 15–20%) in an otherwise asymptomatic child with normal lungs does not usually require evacuation and it spontaneously resolves in about 10–14 days. In symptomatic patients intrapleural air must be evacuated before air travel, as reduced atmospheric pressure during ascent may expand the pneumothorax, increasing the probability of a tension pneumothorax.

In symptomatic patients, mechanical evacuation of the intrapleural air with an intercostal chest catheter insertion using Seldinger technique with underwater seal drainage is warranted. Evidence indicates that small bore chest catheters are equally comparable to large bore catheters in effectively evacuating the intrapleural air. Administering 100% oxygen hastens absorption of the air. The use of suction pressure to expedite air removal is not required in most cases. The initial

use of suction has been associated with increased risk of re-expansion pulmonary edema. Patients with chest catheters in situ should be closely monitored, clinically and with arterial blood gases and analgesics should be prescribed to reduce pleuritic pain. In secondary pneumothorax due to infection, treat with appropriate antibiotics.

Follow-up

Children after pneumothorax drainage in follow-up are monitored for recurrence, lung functions and improvement of lung collapse. Children with primary spontaneous pneumothorax require long-term follow-up for recurrence. Air travel should be avoided for at least 6 weeks.

OTHER AIR LEAK SYNDROMES

Air leaks are usually common in newborn period especially preterms than any other age. In the postsurfactant era, incidence is decreasing. They are also associated with increased risk of intraventricular hemorrhage in preterm neonates.

PULMONARY INTERSTITIAL EMPHYSEMA

It is common in mechanically ventilated children and newborns especially low birthweight babies. Risk factors are low birthweight babies, high peak inflation pressures and malpositioned endotracheal tubes. It manifests with slow deterioration and hypoxemia in ventilated children. Diffuse pulmonary interstitial emphysema (PIE) can increase the risk of bronchopulmonary dysplasia in preterms. It is diagnosed on a radiograph by presence of hyperinflation and cystic lucencies (multiple/small) on the ipsilateral side. There is no definitive treatment. Supportive treatment in the form of use of lower peak inflation and positive end-expiratory pressures and use of high frequency ventilation prevents progression of PIE.

PNEUMOMEDIASTINUM

It occurs when air dissects from the visceral pleura into the connective spaces of the mediastinum. Usually it occurs in association with other air leaks. It presents with tachypnea, desaturation and muffled heart sounds. On the radiograph it manifests as halo of air adjacent to the heart. It is differentiated from pneumopericardium by absence of air beneath the cardiac shadow. On lateral chest film *spinnaker sign* (elevation of thymus by air away from the pericardium) may be seen (**Fig. 2**). It does not require treatment and usually resolves spontaneously.

PNEUMOPERICARDIUM

It occurs when air dissects from the mediastinum into the parietal pericardium through a defect located at pleural reflection near the ostia of pulmonary veins. It presents with features of pericardial tamponade. It can also be differentiated from pneumomediastinum by transillumination—there will be flickering of light with heart rate. Management involves drainage through subxiphoid route; however it is associated with mortality of up to 80%.



Figure 2 Spinnaker sail sign (elevation of thymus by air away from the pericardium) in a neonate with respiratory distress
Source: Varinder Singh.

IN A NUTSHELL

1. Air leak syndromes include pneumothorax, pneumomediastinum, pulmonary interstitial emphysema, pneumopericardium, pneumoperitoneum, and subcutaneous emphysema.
2. Incidence of iatrogenic air leaks has increased with assisted ventilation and other procedures like thoracentesis, tracheostomy.
3. Secondary pneumothorax occurs in presence of underlying lung disease. In a tropical country like India, secondary pneumothorax due to necrotizing pneumonia, especially *Staphylococcus aureus* is one of the most common causes.
4. Clinical presentation and decision to treat pneumothorax mainly depends on age, rapidity of air accumulation, intrapleural pressure and consequent lung collapse.
5. Accuracy of estimation of size of pneumothorax on chest radiographs has not been assessed in pediatric patients.
6. Small bore chest catheters are equally comparable to large bore catheters in effectively evacuating the intrapleural air. Administering 100% oxygen hastens absorption of the air.

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Chapter 39.24

Persistent and Recurrent Pneumonia

Ankit Parakh, Varinder Singh

Pneumonia is clinically defined as combination of respiratory symptoms (cough, dyspnea or tachypnea) and signs (fever, crepitations, focally-reduced breath sounds, fremitus or wheeze).

Persistent or nonresolving pneumonia is defined as the persistence of symptoms and radiographic abnormalities in a child with lower respiratory tract infections (LRTIs) for more than a month despite a course of adequate antibiotic therapy. *Recurrent pneumonia* is defined as at least two distinct episodes of radiologically established pneumonia within the same year or three or more such episodes over anytime period. For the diagnosis of recurrent pneumonia, there must be complete resolution of clinical and radiological findings between acute episodes.

These two entities are sometimes difficult to distinguish clinically and radiologically because the radiographs are usually obtained during acute episodes with no documentation during well periods. While comparing the chest radiographs taken over different times, one must keep in mind that the images may look different not only due to the disease process but also due to variation in the radiological factors, quality and phases of respiration. Given the difficulties in clinically differentiating these two, they are often dealt together. Henceforth, in the present chapter, the term persistent pneumonia shall be used to imply persistent and recurrent pneumonia.

Beyond infections the persistent lung infiltrates can also occur due to various noninfective causes as well. These noninfectious causes have to be teased out carefully. It is equally important to remember that superadded infection could also bring up a patient with an underlying noninfectious etiology, e.g., a congenital pulmonary airways malformation (CPAM) can get recurrently infected.

ETIOPATHOGENESIS

The usual fate of childhood pneumonia is either of the following: recover, slowly resolve, progress, persist, or recur. Most cases of acute childhood pneumonia improve clinically within 5–10 days, while the radiological clearance lags behind. The radiological shadows usually clear within a period of 2–4 weeks, but in a substantial number of children these infiltrates fail to clear completely within 4 weeks.

The rate of resolution of the radiological shadows depends on the causative agent. Infiltrates caused by common viral agents like respiratory syncytial virus (RSV) and parainfluenza virus usually takes 2–3 weeks for clearance, those associated with pneumococcal pneumonia can take 6–8 weeks, and those associated with adenoviral disease can take up to 12 months for clearance. Sometimes the causative organism can leave behind residual radiographic abnormalities (pneumatocoles) like in staphylococcal pneumonia which takes up to weeks to resolve.

For the better understanding of the etiology and pathogenesis, the patients with persistent pneumonia are further divided into those which a single lobe involved and those in which multiple lobes are involved. Infiltrates that recur in a single lobe or segment of the lung may be caused by localized pathology like local airway obstruction—intra/extraluminal, structural abnormalities of airway or lung parenchyma. Multilobar involvement is more

often a result of a systemic problem. Persistent pneumonia usually results from deficiencies in the local pulmonary or systemic host defenses or from underlying disorders that modify lung defenses.

Unilobar Persistent Pneumonia

The causes of unilobar persistent pneumonia can be (1) persistent parenchymal shadow secondary to infections (tuberculosis [TB], hydatid cyst); (2) structural abnormalities: CPAM, sequestration, bronchogenic cysts, hypoplastic lung; or (3) airway obstruction: intraluminal (foreign body, endobronchial TB, endobronchial tumor), luminal (bronchomalacia), extraluminal (enlarged lymph nodes, cardiomegaly, vascular rings). This obstruction leads to local airway narrowing which causes leads to retained secretions in the area distal to the obstruction, impaired mucociliary clearance leading to accumulation of secretions distal to obstruction in which infection supervenes (**Table 1**).

Congenital anomalies such as CPAM, congenital lobar emphysema (CLE), bronchogenic cyst, and pulmonary sequestration, can get infected and lead to recurrent LRTI. Most congenital abnormalities are now diagnosed by prenatal ultrasonography or present shortly after birth as respiratory distress, but can present later in life with recurrent or persistent pneumonia.

Retained foreign body is the most frequent cause of intraluminal obstruction in children age 6 months to 3 years, while TB is the most common cause of infectious lymphadenopathy causing extraluminal compression, leading to chronic or recurrent focal pulmonary disease.

Tracheobronchial tree abnormalities either congenital like tracheal bronchus, bronchial stenosis, or bronchomalacia or acquired conditions like postinfectious bronchiectasis are other important causes. Causes of unilobar persistent pneumonia are listed in **Table 1**.

Multilobar Persistent Pneumonia

Pneumonia that occurs in multiple locations or affects more than one lobe indicates a disease process which is more generalized and therefore a systemic consideration must be taken for evaluation, e.g., primary or secondary immunodeficiency, diffuse alveolar hemorrhage, hypersensitivity pneumonitis, etc. Aspiration into the lung secondary to gastroesophageal reflux (GERD) or anatomical abnormality like cleft or H-type tracheoesophageal fistula (TEF)

Table 1 Causes of unilobar persistent pneumonia

Intraluminal obstruction	Foreign body; endobronchial granuloma—tuberculoma; bronchial tumor—hemangioma, lipoma, adenoma, papilloma
Extraluminal compression	Lymphadenopathy—infectious (tuberculosis, histoplasmosis, etc.) Noninfectious (Malignancy-Hodgkin's disease) Vascular rings and slings Esophageal foreign body Cardiomegaly Inflammatory pseudotumor
Structural abnormalities	Tracheal bronchus Bronchiectasis Right middle lobe syndrome Bronchial stenosis Bronchomalacia may be segmental Congenital pulmonary airway malformation (CPAM) Pulmonary sequestration Congenital lobar emphysema Pulmonary hypoplasia Bronchogenic cyst

Clinical History and Examination

Detailed history includes information regarding the age of onset, frequency, duration and severity of symptoms along with neonatal course, subsequent hospitalizations and operations. History regarding birth problems, developmental delay, feeding problems, immunization status, foreign body aspiration and allergy/atopy needs to be obtained. Family history of any hereditary disorder, sibling deaths, allergy/atopy and environmental history is also important. Physical examination includes vitals, detailed anthropometry along with changes in skin and extremities (cyanosis, clubbing, rashes), any signs of pyogenic infections, presence of conjunctivitis or telangiectasia, ear discharge, sinuses, candidiasis, etc. Detailed systemic examination is also vital. Respiratory system examination—evaluating upper as well as lower airways, cardiovascular system for congenital heart disease, dextrocardia (associated with immotile cilia syndrome), central nervous system for neuromuscular diseases, and abdominal examination for organomegaly is done.

The aim of the earlier evaluation (although sometimes with investigations) is to establish the following:

1. *Does the child truly have recurrent respiratory tract infections?* Many a times children have episodes of recurrent wheezing which with some nonspecific shadows or unrelated shadows in the chest skiagram gets identified as persistent/recurrent pneumonia. They do not need any specific investigations except possibly a lung function testing.
2. *If it is recurrent respiratory tract infections then whether is it based in upper or lower airways or both?* This simple question might require repeated examinations on different occasions.
3. *Is there any involvement of other organ systems?* Multiple organs might be involved in conditions like cystic fibrosis (malabsorption, meconium ileus), immunodeficiency, and primary ciliary dyskinesia (PCD).
4. *Are the frequency and severity of recurrent LRTI sufficient to warrant additional investigations?* The usual indications for evaluating are: more than three episodes of pneumonia in lifetime or more than two episodes over 1 year. The mnemonic *SPUR* is useful to identify those needing further evaluation and this refers to infections that are *severe, persistent, unusual, or recurrent*.
5. Where is the localization of the disease in the lung(s)—unilobar or multilobar?

Investigations

Routine Investigations

These are done as baseline work-up in a case of persistent pneumonia, before deciding the specific investigation which helps in final diagnosis and treatment.

- **Complete hemogram** A complete blood count is used to assess anemia or polycythemia, abnormal numbers, differential makeup of leukocytes and thrombocytopenia (associated with immunological disorders such as Wiskott-Aldrich syndrome (characterized by recurrent infections and autoimmune disorders). Differential count could reveals lymphopenia (seen in RSV infection, acute stress in sepsis, measles infection, *Legionella pneumophila* infection), granulocytopenia (viral infections, drug induced, HIV infection), and eosinophilia (asthma, parasitic infestations, tropical pulmonary eosinophilia).
- **Chest X-ray** Forms an important basis of diagnosis and classification of infiltrates while defining disease, also helps

in confirming the diagnosis, area involved, suggesting etiology and facilitates follow.

- **Investigations for TB** Tuberculin skin test, gastric aspirate or induced sputum for acid fast bacilli (AFB), etc.

Special Investigations

- **Flexible bronchoscopy** In the patients with unilobar involvement, the first in the diagnostic work-up usually is diagnostic flexible bronchoscopy for likely intraluminal obstructive lesions (endobronchial TB, bronchial adenoma, lipoma, foreign body), structural abnormalities like tracheal bronchus, hypoplastic bronchus, etc. Flexible bronchoscopy is a useful investigation also with multilobar pneumonia to evaluate the airways for clefts, H-TEF.
 - A bronchoalveolar lavage can also be taken which could be helpful in identification of pathogen, lipid laden macrophages in aspiration, and hemosiderin laden macrophages in diffuse alveolar hemorrhage. This also makes therapeutic intervention possible like foreign body extraction or biopsy.
- **Contrast enhanced computed tomography (CECT) chest** CECT chest offers several advantages over chest radiography due to its exquisite demonstration of pulmonary architecture without superimposition of overlying structures. CT allows a better assessment of the lesion than is possible on the plain radiograph as it helps in; defining the consistency of lesion—cystic, solid, vascular, in finding or defining a lesion that is obscured by the mediastinum. High-resolution (HR) CT is more sensitive (could detect abnormalities when the chest radiograph was normal); and reportedly showed greater accuracy in characterizing diseases into interstitial, airway and airspace processes; and gave a more accurate depiction of the extent of disease. It is very helpful in evaluation for extrabronchial obstruction, bronchiectasis, distal intraluminal obstructions, structural lesions like sequestrations, congenital cystic adenomatoid malformation (CCAM), etc. The amount of radiation which goes in a CECT chest is equivalent to approximately 50–200 plain radiographs. This hazard should always be considered before ordering this investigation.
- **Further investigations** The guidance for choosing further investigation for children with multilobar pneumonia is less defined and has to be individualized on case to case basis. Children suspected of aspiration syndromes will need a GER scan/24 hour esophageal pH study for GERD, while those with suspected aspiration from above would need a modified barium swallow or video fluoroscopic swallowing studies. Children with findings suggestive of suppurative lung disease would need detailed investigation for cystic fibrosis (sweat chloride estimation, mutation studies, evidence for any metabolic alkalosis), studies for PCD (ciliary studies, Nasal FeNO) and a primary immunodeficiency work-up (detailed in chapter on primary immunodeficiency) or HIV.
 - Pulmonary function tests help to differentiate restrictive from obstructive diseases and have limited utility like for suspected wheezers or interstitial lung disease (ILDs). Spirometry, lung volumes and diffusion capacity; impulse oscillometry for younger children are the modalities used.
 - Echocardiography might be required to rule out cardiac lesions like congenital heart lesions, vascular slings, abnormally dilated heart chambers, etc. which can lead to persistent or recurrent pneumonias. Lung biopsy sometimes might be required in children with suspected ILDs.

IN A NUTSHELL

1. Persistent or nonresolving pneumonia is defined as the persistence of symptoms and radiographic abnormalities in a child with lower respiratory tract infections for more than a month despite a course of adequate antibiotic therapy.
2. Recurrent pneumonia is defined as at least two distinct episodes of radiologically established pneumonia within the same year or three or more such episodes over anytime period.
3. Infiltrates that recur in a single lobe or segment of the lung may be caused by localized pathology like local airway obstruction—intra/extraluminal, structural abnormalities of airway or lung parenchyma. Multilobar involvement is more often a result of a systemic problem.
4. Besides routine investigations, the child may require a fiberoptic bronchoscopy, CECT chest, pulmonary function tests, and investigations to rule out immunodeficiency, GERD, cystic fibrosis or congenital heart disease.

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Chapter 39.25

Interstitial Lung Disease

A Bush

Childhood interstitial lung disease (chILD), sometimes termed as diffuse lung disease (DLD) comprises a rare and disparate group of disorders about which very little is known in any setting, least of all in the developing world. Around 200 different entities have been described under its umbrella, and undoubtedly many more will be found. Pathologically, chILD may result in any or all of filling of the alveolar spaces; and inflammation and fibrosis in the interstitium of the lung and the distal most airways. The barrier between very distal airway disease and the lung disease which is truly confined to the interstitium, is blurred in most classifications.

Why then are these rare and esoteric diseases important to pediatricians in a developing world setting, or general pediatricians in any setting? Firstly, they mimic many pediatric respiratory conditions, and a correct diagnosis will mean that inappropriate treatments are not given, and allow specific therapies to be utilized, which may be dramatically effective in some cases. A diagnosis of a genetic cause of chILD has implications for the extended family. The general pediatrician will have a key role supporting the family and collaborating with the specialist center. Identification of an unusual chILD may mean that a novel environmental agent, specific to a particular region, is implicated, allowing prevention and treatment. This is definitely an area where all pediatricians and all parts of the world need to learn together.

EPIDEMIOLOGY

The data are at best an approximation. Compared with adult ILD prevalence of 60–80/100,000, the estimated prevalence of chILD in the developed world is 0.36/100,000. The most common age of presentation is 0–2 years. There are no reliable developing world data, in part due to the difficulty of establishing the diagnosis. Given the many potential genetic and environmental causes, and the differences in the environments and parental consanguinity across the world, these figures should not be extrapolated uncritically from where they were obtained. However, an unexpected upsurge of cases should trigger a search for a new causative agent.

ETIOLOGY

There are numerous causes of chILD and a discussion of all is beyond the scope of this chapter. It should be noted that overlaps are not uncommon; and more than one histological pattern may be present. In general, classifications report 0 to less than or equal to 2 years and 2–16 years separately, although in fact many conditions are common to both. Many classifications are based solely on lung biopsies, and thus exclude conditions which very appropriately may not come to biopsy.

Etiology in the First 2 Years of Life

- *Diffuse developmental disorders:* A spectrum of alveolar-capillary dysplastic disorders, presenting with neonatal respiratory distress in a term baby, which are usually rapidly fatal.
- *Growth disorders:* The pulmonary hypoplastic syndromes, in which some include bronchopulmonary dysplasia (which is not usually difficult to diagnose).
- *Conditions specific to infancy:* Neuroendocrine cell hyperplasia of infancy (NEHI) usually presents with tachypnea and

hypoxemia; high-resolution computed tomography (HRCT) shows ground glass shadowing in the perihilar regions, middle lobe and lingula. If lung biopsy is performed, it looks normal but if appropriately stained, increased numbers of cells positive for the neuropeptide bombesin are seen. Pulmonary interstitial glycogenosis (PIG) has a similar presentation, HRCT is nonspecific and biopsy shows the interstitium to be widened by glycogen containing (PIG) cells. PIG is unrelated to any glycogen storage disease. It should be noted that PIG and NEHI cells are found during normal lung development, and also in other chILD.

- *Surfactant protein (Sp) gene mutations* *Sp-B* and *Sp-C* are responsible for maintaining alveolar surface tension, *Sp-A* and *Sp-D* being part of the collectin system. chILD is caused by mutations in *Sp-B* and *Sp-C*, in *ABCA3* (responsible for post-translational modification of *Sp*, and thyroid transcription factor-1 (*TTF-1*), a transcription factor for the other three genes; this last may be associated with brain and thyroid disease.
- *Pulmonary alveolar proteinosis:* There are numerous underlying causes in children, including the *Sp* mutations, mutations in the granulocyte-macrophage colony-stimulating factor (GM-CSF) receptor gene, GM-CSF autoantibodies, metabolic diseases such as lysinuric protein intolerance, and immunodeficiency.
- *Disorders of the normal host:* Airway diseases, aspiration (which may coexist with chILD) and hypersensitivity pneumonitis.
- *Disorders of the immunocompromised host:* Which may be the first presentation of the immune deficiency, or occur in a child with known immune compromise.
- *Mimics of chILD* (see later).
- *Unclassifiable:* The biopsy is technically unsatisfactory, or merely shows end-stage fibrosis.

Child Age 2–16 Years

- *Disorders seen in infancy:* May present at this age, especially *Sp* gene mutations (*Sp-C*, *ABCA3* and *TTF-1*); indeed around 25% come into this category.
- *Airway disease:* Follicular bronchiolitis (which may be associated with immunodeficiency), and chronic bronchiolitis negative for NEHI cells.
- *Lymphoproliferative disorders:* Associated with immunodeficiency, e.g., lymphoid interstitial pneumonia (LIP).
- *Miscellaneous:* Diffuse diseases (hemosiderosis, hypersensitivity pneumonitis, sarcoidosis, Langerhans cell histiocytosis and pulmonary alveolar microlithiasis).
- *Mimics of chILD:* chILD complicating systemic disease, vascular disease, other disorders of the normal host.

These groupings are by no means exhaustive in either age range.

PATHOGENESIS

Little is known about the exact pathophysiology in children. *Sp* gene mutations that increase oxidative stress in the endoplasmic reticulum may lead to cell damage. At least some *Sp-C* mutations lead to increased cytotoxicity of viruses, particularly respiratory syncytial virus (RSV); and nearly half such patients present with nonresolving RSV bronchiolitis. There are animal and cellular models, for example GM-CSF autoantibody disease, but as yet they have not delivered clinically relevant data. A little more is known about hypersensitivity pneumonitis. Here an allergen is thought to trigger an exaggerated mixed Type 3/Type 4 immunological response because of a genetic predisposition, leading to a

granulomatous inflammation. If the antigen exposure is chronic and low-grade, then presentation is with a fibrotic picture.

CLINICAL FEATURES

Presentation is nonspecific. In one large series, the most common presenting symptoms and signs were hypoxia, tachypnea, retractions, gastroesophageal reflux (GER), pulmonary hypertension, cough, crackles, wheeze and failure to thrive. Chest auscultation may be normal. The chest radiograph is nonspecifically abnormal, and may reveal diffuse ground glass appearance, or bilateral patchy abnormalities, or may even be normal. Further detailed investigation is essential. Childhood ILD should also be suspected in the following circumstances:

- Positive family history of unexplained respiratory disease
- The term baby with progressive respiratory distress from birth
- The baby with bronchiolitis which fails to resolve as expected
- Iron deficiency anemia when all common causes have been excluded; suspect chronic pulmonary hemorrhage.

Childhood ILD may present with acute onset of respiratory failure; examples are acute pulmonary hemorrhage and acute hypersensitivity pneumonitis, when a big antigen load is inhaled.

DIFFERENTIAL DIAGNOSIS

The nonspecific presentation implies that virtually any subacute or chronic pediatric respiratory condition may mimic chILD. The most likely diagnoses will depend on the patterns of disease in the region.

- *The term baby with progressive respiratory distress:* Consider congenital infections, persistence of the fetal circulation, congenital heart disease, meconium and other aspiration syndromes, primary ciliary dyskinesia, pulmonary hypoplastic syndromes, and severe immunodeficiency.
- *The baby with nonresolving bronchiolitis:* Infection with adenovirus or other causes of obliterative bronchiolitis; immunodeficiency including HIV and cystic fibrosis.
- *Pulmonary hemorrhagic syndromes:* Congenital heart disease, coagulopathy.
- *Acute onset of breathlessness* without wheeze is most usually due to acute asthma, but remember the acutely presenting chILDs.

APPROACH TO DIAGNOSIS

These children require a detailed evaluation. The tempo of the approach depends on the degree of illness of the child, and is a matter of judgment. The availability of tests is also a factor; if, for example, *Sp* gene mutation and other testing is not available, it may be justifiable to go on to blind treatment trials. In a child who is stable in low-flow oxygen, it may well be justified to await the results of blood tests, whereas in a rapidly deteriorating child, urgent lung biopsy or empirical treatment (later) may be the correct approach.

If chILD is a possible diagnosis, the next step is HRCT scanning. HRCT should only be performed by an experienced

pediatric radiologist with due care to minimize radiation exposure and maximize image quality. Indications for HRCT are as follows:

- To confirm the presence of chILD, or conversely, reveal an unexpected and different pathology.
- Occasionally, a specific diagnosis can be made (e.g., Langerhans cell histiocytosis, hypersensitivity pneumonitis) or a specific pattern identified (e.g., the cobblestone appearance of pulmonary alveolar proteinosis) but usually the pattern is either suggestive but not necessarily diagnostic (e.g., NEHI) or more usually, non-specific.
- If the child does come to a diagnostic lung biopsy, then the HRCT is used to guide the optimal site of the biopsy.

The next step is to score the severity of the disease (**Table 1**). In an older child, lung function testing may reveal a restrictive pattern of spirometry, reduced lung volumes, and usually reduced carbon monoxide transfer (DLCO). If DLCO is elevated, alveolar hemorrhage should be suspected. The most widely used severity score involves measuring the child's saturations overnight, and on exercise, and also performing an echocardiogram. This last test is not merely to document whether pulmonary hypertension is present, but also to exclude cardiac mimics of chILD, such as any condition causing left atrial hypertension. The choice of blood tests depends on the clinical context; options are listed in **Table 2**. It would clearly be out of context to look for surfactant protein gene mutations in a boy with a history and HRCT classical for hypersensitivity pneumonitis, or look for positive precipitins in a term baby ventilated from birth; good clinical judgment is mandatory.

At this point it is important to reach a decision as to whether bronchoscopy or lung biopsy is indicated. As with all tests, the key question is, what action may result as consequence? So in a baby who is stable and thriving in a small amount of oxygen, with HRCT strongly suggestive of NEHI, it is likely no treatment will be offered irrespective of the results of invasive tests, and so these should not be performed. If invasive testing is being considered, then this should be planned to minimize the number of general anesthetics for the child. Indications for bronchoscopy are:

- Suspected opportunistic infection in a child known to have or with suspected immunodeficiency.
- Confirm pulmonary hemorrhage (hemosiderin laden macrophages) or pulmonary alveolar proteinosis (milky bronchoalveolar lavage [BAL] fluid).

However, for the most part the findings are nondiagnostic, and for most chILD, bronchoscopy is legitimately performed at the time of lung biopsy, but not as a separate procedure.

The ultimate diagnostic procedure is lung biopsy, usually video-assisted thoracoscopic surgery (VATS) or via a mini-thoracotomy. Transbronchial biopsy is not recommended in the context of chILD; the samples are usually too small, unless a very specific pattern such as pulmonary alveolar microlithiasis is present, and there is a definite risk of hemorrhage and pneumothorax. It is essential that there is discussion with the surgeon about the site of biopsy, and also that the tissue is handled correctly after the biopsy, so that electron microscopy and all necessary stains can be performed. It is often wise to get more than one opinion on pathology in these rare conditions.

Table 1 Illness severity score used in childhood interstitial lung disease (chILD)

Score	Symptoms	Hypoxemia < 90% sleep or exercise	Hypoxemia < 90% rest	Pulmonary hypertension
1	No	No	No	No
2	Yes	No	No	No
3	Yes	Yes	No	No
4	Yes	Yes	Yes	No
5	Yes	Yes	Yes	Yes

Table 2 Blood tests to be considered in the work-up of interstitial lung disease (ILD) in children. Not all should be performed in all cases

Test	Disease	Comment
<i>Sp-B, Sp-C, ABCA3, TTF-1</i> genes	Surfactant protein deficiency	Indicated in most children with ILD, unless there are extrapulmonary features or another obvious diagnosis
Angiotensin converting enzyme	Sarcoidosis	Especially if extrapulmonary features
Antineutrophil cytoplasmic antibodies	Wegener granuloma, other vasculitides	Especially if upper airway disease, renal disease, pulmonary hemorrhage
Avian, <i>Micropolyspora faeni</i> precipitins	Allergic alveolitis	CT scan may be suggestive of this diagnosis
Viral and mycoplasma serology	Obliterative bronchiolitis	Not a true ILD, but may be confused on CT
Immune work-up including HIV	Lymphoproliferative syndromes, including follicular bronchiolitis	Also perform if ILD in fact proves to be an opportunistic infection
Autoantibody studies	Systemic lupus, rheumatoid diseases, scleroderma, and other collagen vascular disease	Especially if extrapulmonary features and renal disease
GM-CSF studies (serum autoantibody, receptor genetic studies)	Some of the variants of pulmonary alveolar proteinosis	Adult type with response to GM-CSF has been described in children

Abbreviations: CT, computed tomography; HIV, human immunodeficiency virus; *Sp*, surfactant protein; *TTF*, thyroid transcription factor; GM-CSF, granulocyte-macrophage colony-stimulating factor.

MANAGEMENT

General Considerations

There are no randomized controlled trials of treatment in chILD. If the child is hypoxic, then oxygen should be given; this is probably the only noncontroversial statement to make. All immunizations including influenza should be given unless contraindicated, and the child protected from environmental tobacco smoke as well as other pollutants. Nutrition needs to be optimized; a number of chILD patients have swallowing and feeding issues, for which early referral is essential.

Specific Therapy

Childhood ILD for whom No Treatment is Available

One of the reasons for pursuing a specific diagnosis is that there are conditions in which steroids are ineffective (e.g., NEHI and PIG) or actually harmful (opportunistic infections).

Treatments for Childhood ILD

If the decision is taken to treat the child, and there is no specific therapy available, then the backbone of empirical treatment is systemic steroids. If there are no facilities to confirm a specific diagnosis through lung biopsy, or the child is judged too sick for the procedure, then blind treatment may be justifiable. Indeed, some authorities treat all patients blindly, reserving biopsy for the steroid nonresponsive cases. One preferred (nonevidence based) regime is pulsed intravenous methyl prednisolone 10 mg/kg on 3 successive days every 4 weeks, combined with hydroxychloroquine 10 mg/kg and azithromycin 10 mg/kg, both once daily. One could use this regime for 6 months in the first instance. Children with severe ILD may mandate maintenance prednisolone (0.5 mg/kg on alternate days) between pulses, tapering as the disease permits. As an alternative to pulsed methyl prednisolone, oral daily prednisolone 2 mg/kg/day can be used, tapering the dose where there is a response. If there is no response to these steroid based regimes, empirical trials of cytotoxics such as methotrexate or azathioprine, or biologicals such as rituximab may be attempted. There is no role for inhaled corticosteroids.

Childhood ILD for which there are Specific Treatments

- *Hypersensitivity pneumonitis*: The key is identification of the allergen and prevention of exposure, in addition to steroid therapy (pulsed or oral, as earlier).

- *Sarcoidosis*: The antitumor necrosis factor- α (TNF- α) monoclonal infliximab, combined with methotrexate, may be effective.
- *Pulmonary alveolar proteinosis*: If due to anti-GM-CSF auto-antibodies, then inhaled or subcutaneous GM-CSF is effective, albeit expensive; whole lung lavage, which may need to be repeated on multiple occasions, may also work well.
- *chILD secondary to rheumatological conditions* may respond to specific regimens, e.g., cyclophosphamide for granulomatosis with polyangiitis (formerly known as Wegener's granulomatosis).
- *Idiopathic pulmonary hemosiderosis*: If bleeding is not controlled on the nonspecific regime above, consider triple pulses of intravenous immunoglobulin, intravenous cyclophosphamide and methyl prednisolone. Plasmapheresis can be used if acute bleeding continues despite steroid pulses; again, there is not much evidence for this.

Monitoring the Response to Therapy

There are no known biomarkers specific to chILD, and no guidelines on how to monitor the disease. If the child is old enough to perform lung function tests, and these are available, then spirometry may be used. Otherwise, oxygen requirement is a useful parameter, including the extent and speed of desaturation in room air. Repeat HRCT may be used to help judge the need for repeated lung lavage in pulmonary alveolar proteinosis, but otherwise is probably not as useful as physiological parameters.

Family Support

The family's anxieties must be understood; there may be a need for counseling or emotional support. They may need help in managing expectations in terms of the long-term prognosis. All parents feel scared and anxious about the future of chILD but with effective communication, fears can be faced. There must be a support system for the family, and an established point of contact if things are going wrong. If one is available, refer early to a pediatric respiratory specialist. The overall holistic care of the child, focusing not just on the disease, but the child and family, is a key role for all pediatricians. Finally, put the family in touch with others; if there is no national support group, the UK (<https://childlungfoundation.org>) and the USA (<http://www.child-foundation.com/>) have excellent parent support groups which can help families who are feeling alone and isolated.

OUTCOME

It is often very difficult to give an accurate prognosis, because most series of individual conditions are very small. So for example *Sp-C* mutations have a very variable phenotype, ranging from severe neonatal respiratory distress to usual interstitial pneumonitis in late middle age. Thus caution is indicated. Outcome of few specific conditions is as follows:

- **NEHI:** Oxygen dependency may be prolonged for many years, but eventual resolution should be anticipated. There may be persistent airflow obstruction, unresponsive to asthma medications.
- **PIG:** Prognosis is good, but deaths have been reported in preterm babies with this condition.
- ***Sp-B* mutations:** Although very rare, partial deficiencies with a good prognosis have been described, in general most die or have to be transplanted within a few months of birth.
- **Other *Sp* mutations:** As a general rule, the earlier the presentation, and the more severely ill the child, the worse the outlook.
- **Acute hypersensitivity pneumonitis:** If allergen exposure can be controlled, these children are usually steroid sensitive and a good recovery can be anticipated. However, if a fibrotic stage has been reached, then stabilization rather than recovery is the best that can be hoped for.
- **Pulmonary hemorrhagic syndromes:** The prognosis is very unpredictable, and even severely ill children may go into remission.

PREVENTION

There are no primary preventive strategies for chILD. Secondary prevention can be achieved in genetic chILD by termination of future affected pregnancies if this is acceptable to the families, and prevention of allergen exposure in cases of hypersensitivity pneumonitis.

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IN A NUTSHELL

1. Childhood interstitial lung disease (chILD) comprises a rare and disparate group of more than 200 different entities.
2. Pathologically, chILD may result in filling of the alveolar spaces; and inflammation and fibrosis in the interstitium of the lung and the distal most airways.
3. Etiology in the first 2 years of life primarily consists of diffuse developmental disorders, neuroendocrine cell hyperplasia of infancy (NEHI), pulmonary interstitial glycogenosis, surfactant protein (*Sp*) gene mutations, and pulmonary alveolar proteinosis.
4. After 2 years of age, causes of ILD include *Sp* gene mutations, follicular bronchiolitis, lymphoid interstitial pneumonia (LIP), hemosiderosis, hypersensitivity pneumonitis, sarcoidosis, Langerhans cell histiocytosis and pulmonary alveolar microlithiasis.
5. Presentation is nonspecific. The most common presenting symptoms and signs are hypoxia, tachypnea, retractions, gastroesophageal reflux, pulmonary hypertension, cough, crackles, wheeze and failure to thrive.
6. HRCT chest, *Sp* gene mutation, lung function testing, Echo, CT, and bronchoscopy help in making the diagnosis. The ultimate diagnostic procedure is lung biopsy, usually VATS or via a mini-thoracotomy. Transbronchial biopsy is not recommended.
7. The backbone of empirical treatment of chILD is systemic steroids.

Chapter 39.26

Hemoptysis and Alveolar Bleeds

Meenu Singh, Nandini Paul

HEMOPTYSIS

Hemoptysis is defined as the coughing up of blood or blood-streaked sputum from the respiratory tract because of hemorrhage in the lungs. The criteria for categorization of hemoptysis are not well-established, yet it can be categorized as nonmassive or massive depending upon the amount of blood loss. Blood loss of 200 mL/day is categorized as massive hemoptysis and is considered as life-threatening. The diagnosis of hemoptysis in younger children becomes difficult because of their inability to expel out the sputum. The most common causes of hemoptysis in children are bronchiectasis, fungal infections and tuberculosis (**Table 1**). In European population, the most common predisposing factor for hemoptysis is cystic fibrosis.

ALVEOLAR BLEEDS

Alveolar bleeds refer to alveolar hemorrhage, a rare state of the airways, in which blood is infiltrated at multiple sites into the alveoli. The synonymous terms include: pulmonary alveolar hemorrhage, diffuse pulmonary hemorrhage, pulmonary capillary hemorrhage, microvascular pulmonary hemorrhage or alveolar bleeding. It is usually associated with anemia and hemoptysis but at times these conditions may be absent.

Localized pulmonary hemorrhage is a similar clinical condition which must be distinguished carefully. Accumulation of red blood cells (RBCs) originating from the alveolar capillaries into the alveoli is the characteristic feature of alveolar hemorrhage. On the other hand, localized pulmonary hemorrhage is confined to a particular region of the lung. Hemoptysis, a condition most often associated with alveolar hemorrhage, may not be present always but it should be tracked by bronchoalveolar lavage analysis with worsening RBC count. The condition may get worsened requiring ventilation and radiographic procedures.

EPIDEMIOLOGY AND ETIOLOGY

The prevalence of pulmonary hemorrhage in neonates has been found to be 7–10% upon postmortem examination. The incidence of pulmonary hemorrhage in live births is 1 out of 1,000. The etiology of the alveolar hemorrhage includes both immune-mediated and nonimmune-mediated disorders. The lungs are supplied by two

circulatory systems: the bronchial circulation is a high-pressure circuit arising from aorta and supply blood to the terminal bronchioles, whereas the pulmonary circulation is a low-pressure and high-capacitance circuit that arises from the right ventricle and perform gas exchange. The hemorrhage due to any of these circulation systems can be the result of multiple causes and may be localized or diffuse. Acute lower respiratory infection is the most common trigger, responsible for almost 40% of cases. Respiratory infections cause inflammation of the mucous membranes resulting into the breaking of the blood vessels. In children, airways infection with viruses, bacteria, fungi (aspergilloma) and parasitic diseases may also lead to hemoptysis. Hemoptysis due to tuberculosis is not as common in children as in adults but can be seen among adolescents with fibrocavitary disease. Children with cystic fibrosis often present with hemoptysis because of severe chronic airway inflammation that ultimately leads to progressive bronchiectasis and increased dilatation and fragility of bronchial vessels in the airway walls. Moreover, bronchiectasis related to other complications such as primary ciliary dyskinesia or immunodeficiency can also lead to bleeding. Colonization of the airways with microbes exacerbates these underlying diseases and forceful cough contributes to bleeding. Pulmonary hydatidosis is another important cause for hemoptysis.

Lung anomalies like pulmonary arteriovenous (AV) malformations, pulmonary telangiectasia, congenital absence of pulmonary veins, sequestrations also present as hemoptysis. Neglected congenital cyanotic heart disease cases like tetralogy of Fallot may present with hemoptysis due to rupture of large intrapulmonary collaterals. Severe mitral stenosis can also present with breathlessness and hemoptysis and is usually seen with poorly managed rheumatic heart disease.

Hemoptysis should not be confused with the bleeding from the upper digestive tract, nasopharynx and oropharynx. This condition is referred to as pseudohemoptysis. *Factitious hemoptysis* is another condition associated with unusual symptoms and a negative evaluation.

A number of diseases have been found to be responsible for alveolar hemorrhage. Although there is no prospective study that has identified the actual reason behind alveolar hemorrhage, yet various studies propose idiopathic pulmonary hemosiderosis, Wegener granulomatosis, microscopic polyangiitis, collagen vascular disease and Goodpasture syndrome as the most common conditions responsible for it.

PATHOPHYSIOLOGY

Pathophysiology is varied just as the causes are. The lung is made up of two vascular systems: (1) the pulmonary system and (2) the bronchial system. Hemoptysis and alveolar hemorrhage can occur in any of these systems. Hemoptysis may be due to various underlying diseases ranging from cardiovascular disease to pulmonary disease. Diseases associated with diffuse alveolar hemorrhage (like idiopathic pulmonary hemosiderosis, Wegener granulomatosis, microscopic polyangiitis, collagen vascular disease, Goodpasture syndrome and pulmonary capillaritis) are likely to have neutrophil infiltration into the alveoli and bronchioles causes breakage of capillaries which further results into infiltration of RBCs in the alveolar region. Recurrent alveolar hemorrhage can further progress to pneumonia, deposition of collagen in the smaller airways, and ultimately to fibrosis or respiratory failure.

CLINICAL FEATURES

The clinical symptoms of alveolar hemorrhage include alveolar bleeding or those related to the underlying cause. The common initial symptoms include dyspnea, cough, and fever often along

Table 1 Common causes of hemoptysis

<i>Respiratory</i>
• Respiratory tract infections—pneumonia, tracheobronchitis, pharyngitis, tuberculosis
• Cystic fibrosis
• Foreign body aspiration
• Nasopharyngeal bleeding
• Bronchiectasis
• Pulmonary neoplasms
• Carcinoma
<i>Others</i>
• Congenital heart disease
• Cysts in lungs
• Unknown causes

with hemoptysis. Sometimes hemoptysis may go unnoticed initially, because the alveoli absorb a large volume of the blood. A careful record helps in differentiating between hemoptysis, pseudohemoptysis, and hematemesis. The most common causes in pediatric patients include: infections of the lower airways and foreign body aspiration, whereas cystic fibrosis and bronchiectasis are secondary causes. Bronchitis, pneumonia and lung carcinoma are the major causes in adults.

DIAGNOSIS

Hemoptysis

Diagnostic approach for hemoptysis consists of following steps:

- Clinical records of the patients for past history of the present symptoms and associated family history.
- Assessment of blood loss consisting of duration, frequency and amount of blood and whether the blood was expelled by coughing or vomiting.
- Sputum sample analysis for confirming hemoptysis.
- Radiographic examination consisting of chest X-ray, high resolution computed tomography (HRCT) scan, bronchial angiography.
- Laboratory testing includes blood tests for WBC analysis and cells morphology in sputum and culture and bacterial identification tests.
- Bronchoscopy and bronchoalveolar lavage (BAL) for hemosiderin-laden macrophages (HLM).

Alveolar Hemorrhage

The diagnosis of alveolar hemorrhage largely depends upon clinical features of underlying disease. The most common clinical features involved are dyspnea, cough, hemoptysis, and new alveolar infiltrates along with blood-stained BAL specimens (containing numerous erythrocytes and siderophages). Unlike bleed from the airway disease like bronchiectasis, these cases often do not have significant cough or sputum production. As the symptoms are not specific in nature, the recognition of alveolar hemorrhage often requires BAL analysis. Gross hemoptysis is absent in up to one-third of patients and they may be identified by detecting blood tinged BAL during interval fiberoptic bronchoscopy. The diagnosis of alveolar hemorrhage is a tedious task as the symptoms are nonspecific nature. A number of factors are taken into consideration while making the final diagnosis, i.e., clinical features, radiographic procedures (HRCT and pulmonary arteriogram) and bronchoalveolar analysis. After the correct diagnosis is established, the underlying cause of the condition must be targeted to initiate the therapeutic process.

MANAGEMENT

Management of alveolar hemorrhage and hemoptysis aims at protecting the airways; and maintaining the structure of the airways, oxygen content and blood volume. Treatment largely depends upon underlying cause of the disease and it should be worked up properly. Cough suppressants can be used for minor hemoptysis, whereas tuberculosis is treated with anti-tubercular therapy. Infections are to be treated appropriately as per etiology.

For the therapy of idiopathic pulmonary hemosiderosis, prednisolone is used with or without hydroxychloroquine. Corticosteroids and immunosuppressive drugs are the therapy of choice and remain the gold standard for the treatment of other conditions with diffuse alveolar hemorrhage like Wegener's granulomatosis. At times when corticosteroids become less effective, other immunosuppressive drugs are used as therapeutic regimens including cyclophosphamide, azathioprine, etanercept

and mycophenolate mofetil. Other protective strategies such as oxygen supplementation, use of bronchodilators and intubation with bronchial tamponade are also used when lung damage is less.

Various techniques are used for the treatment of massive hemoptysis due to bronchial bleed seen with bronchiectasis of varied causes. These include CO₂ laser bronchoscopy, endoscopic tumor excision, vasoconstriction therapy, and lobectomy. In case if hemorrhage continues even after endoscopic measures, then emergency arteriography is done. Severe hemoptysis is managed by bronchial artery embolization (BAE). This technique demands angiographic skills and is a challenging task that is not always available in pediatric settings. Moreover, it is associated with neurological damage due to embolization of spinal arteries.

PROGNOSIS

The prognosis of alveolar hemorrhage and hemoptysis is largely based on the underlying cause of the condition. Repeated incidents of hemorrhage may further cause interstitial fibrosis and respiratory failure. Identification of underlying cause is necessary for proper therapy. Diagnosis of underlying cause plays an important role in the management of massive hemoptysis (> 1,000 mL blood volume within a day). The mortality rate depends upon the underlying condition. Bronchiectasis and bronchitis are at low risk of mortality as compared to patients with tuberculosis and pulmonary carcinoma.

IN A NUTSHELL

1. Alveolar hemorrhage and hemoptysis are the critical conditions. The severity depends upon the associated medical problems.
2. The diagnosis of such conditions at early stage and prior treatment is required to prevent the progressive damage to the airways.
3. There remains a lot of ambiguity on the therapeutic regimens. Further research is needed to reveal the proper treatment modalities.

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Chapter 39.27

Primary Ciliary Dyskinesia

Ada Y Yip, Daniel K Ng

Primary ciliary dyskinesia (PCD) refers to primary defect in structure or function of cilia leading to their dysmotility or immobility. Dynein arms defects account for more than 80% of cases. PCD is characterized by chronic upper and lower respiratory tract infection with or without mirror image arrangement. The well-known triad of sinusitis, bronchiectasis and situs inversus is called Kartagener syndrome. Among those with PCD, 48% have situs inversus.

Secondary cilia changes are defects in cilia structure found in up to 3% of ciliated cells of a healthy individual. The percentage would be higher after exposure to pollutant, infection or inflammation. Inner dynein arm and radial spokes defects are commonly seen. They must be differentiated from primary defect by repeating diagnostic test with a new sample that is taken 4–8 weeks later, the turnover time of respiratory epithelium.

EPIDEMIOLOGY

In Europe, prevalence of PCD is 1:15,000–1:30,000 live births, but a wide variation among different European countries has been reported. A cohort study conducted by O'Challaghan et al., has showed that PCD can be as common as 1:2265 in a British Asian in Bradford. PCD is largely inherited in an autosomal recessive manner. Autosomal dominant or X-linked inheritance is also reported.

ETIOLOGY

Primary defect in cilia results in generalized functional impairment of ciliated cells in their propelling functions, resulting in stasis of mucus in the sinuses, middle ear, respiratory tract or impaired movement of sperms or fertilized ovum resulting in sinusitis, otitis media with effusion, bronchiectasis, infertile male and ectopic pregnancy, respectively.

Cilia are complex structure made up of more than 200 polypeptides. The protein size is large and the genetic make-up was diverse. DNAI1 mutation accounts for ~10% of PCD and DNAH5 mutation accounts for ~20% of PCD. Both of them account for 20–40% of PCD patients with outer dynein arm defect. A mutation at DNAI1V5+2_3insT is responsible for more than 50% of mutations. Other mutations like DNAH5, DNAI1, DNAI2 are also associated with outer dynein arm defect. KTU and LRRC50 are associated with combined dynein arm defect. DNAH11 is associated with situs inversus but not dynein arm defect. RPGR is associated with X-linked retinitis pigmentosa and sensory hearing deficits. The above list is not exhaustive and many more genes are yet to be discovered in this genetically heterogeneous disease.

PATHOPHYSIOLOGY

Cilia are organelles that consist of hundreds of polypeptides. Most cilia have a typical 9+2 ultrastructure (**Fig. 1**), i.e., 9 microtubule doublets (microtubule A and B) surrounding a pair of central singlet microtubules. Each of the peripheral doublets is linked to their adjacent pair by nexin links and is connected to the central pair microtubules by radial spokes. Inner and outer dynein arms are ATP-containing units that are located on microtubule A and are responsible for sliding along adjacent microtubule B during movement. Nexin links and radial spokes restrain the degree of sliding and cause cilia to bend. Cilia are classified into motile cilia, nodal cilia and primary cilia.

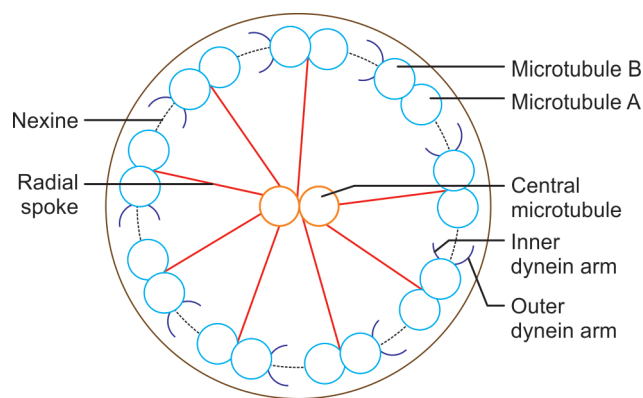


Figure 1 9+2 ultrastructure of cilia

Motile cilia have 9+2 ultrastructure. They line the surface of nasal cavity, sinuses, middle ear, eustachian tube and tracheobronchial tree. About 200 cilia are found on apical surface of each epithelial cell and they beat synchronously at a natural frequency of 8–20 Hz to form a metachronal wave. Each cilium beat cycle consists of a powerful effective stroke that propels mucus forward and a slow recovery stroke that brings cilium back to its original position along the same plane. Any defect that impairs cilia beat frequency, beat coordination or change in chemophysical nature of mucus (like cystic fibrosis) will result in impaired mucociliary clearance. Mucus pooling predisposes to infection and causes rhinosinusitis, otitis media, glue ear, bronchitis, pneumonia, and bronchiectasis. Motile cilia are also found on ependyma, Fallopian tube and flagella of sperm; defect of which will result in hydrocephalus, ectopic pregnancy and infertility respectively.

Nodal cilia are the only motile cilia found at embryonic stage. They have 9+0 configuration as they lack central microtubules and have a unidirectional rotatory movement that result in leftward flow of extracellular fluid, which is important in signaling left-right orientation. Any defect in nodal cilia function will result in random organization of internal organ, causing left-right laterality problem, found in nearly half of the cases with PCD. This includes situs inversus totalis (48%), situs ambiguus (6%), abdominal organs and pulmonary situs abnormalities.

Primary cilia are immotile cilia with 9+0 ultrastructure and no dynein arms. They are mono-cilia and are found in many organs including eyes, liver, kidney, etc. Some of them have sensory function and act as photoreceptors and olfactory receptors. Defect of primary cilia may result in a wide variety of diseases like tracheoesophageal fistula, severe esophageal reflux, biliary atresia, polycystic kidneys, abnormal leukocyte function, rheumatoid arthritis, etc.

CLINICAL PRESENTATION

Newborns with family history of PCD, persistent rhinitis (76% of PCD), unexplained tachypnea or respiratory distress due to delayed removal of lung fluid after birth (> 75% of PCD) and left-right laterality problem like situs inversus (40–50% of PCD), heterotaxy (6% of PCD), isomerism or dextrocardia warrant an early investigation for PCD. Chronic rhinosinusitis, otitis media, otitis media with effusion (51% of PCD) resulting in conductive hearing loss, chronic wet cough (universal), wheeze, protracted bronchitis and recurrent pneumonia are common clinical features in childhood. Digital clubbing and bronchiectasis are present in 83% of adults with PCD. Half of the affected adult males are infertile due to impaired spermatozoa motility, while adult females

are usually subfertile with an increased risk of ectopic pregnancy because of impaired Fallopian tube transport. Other presentations like hydrocephalus, severe gastroesophageal reflux and biliary atresia are rarely seen.

DIFFERENTIAL DIAGNOSES

Differential diagnoses mainly cover the diagnoses leading to bronchiectasis or persistent bacterial bronchitis. They include immunodeficiencies (congenital or acquired), gastroesophageal reflux with or without aspiration, dysfunctional swallowing, and structural airway lesion like tracheoesophageal fistula.

APPROACH TO DIAGNOSIS

Saccharin Test

Saccharin test has been used for many years as a crude assessment of mucociliary function. It is done by putting a saccharine micro-tablet on the inferior turbinate of an individual who sit-still and inclined forward. No coughing, sniffing or swallowing is allowed. Saccharin is expected to be tasted within 60 minutes. Failure or delay in tasting is suggestive of abnormal ciliary function. This test is limited by the fact that it is unreliable in young children less than 6 years old, hence unable to aid diagnosis in half of the cases as median age for PCD diagnosis is 5.3 years old and cilia with dyskinetic movement will be missed. Few centers now instead look for a migration of a small amount of gel containing radioactive material in the anterior nares to confirm presence or absence of ciliary movements.

Nasal Nitric Oxide Test

Nasal nitric oxide (NO) is produced by nitric oxide synthase mainly from paranasal sinus epithelium. It is present in high concentration in the upper respiratory tract and is believed to have a role in local defense against microbes, cilia motility regulation, effect on bronchial tone and pulmonary vascular resistance. Extremely low (about 10% of normal) nasal NO level is detected in PCD. If nasal NO level is more than 150 ppb, PCD can be excluded with certainty.

Ciliary Studies

A complete assessment of cilia ultrastructure is possible by transmission electron microscope (TEM), assessment of ciliary beat frequency, pattern and coordination of movement. When necessary, cilia should be cultured to get rid of damages secondary to infection and inflammation for analysis. All these testes required a high degree of expertise and should be performed in centers experienced in taking care of patients with PCD.

Electron microscopy Cilia ultrastructure can be assessed by TEM. Most commonly encountered structural defect is outer dynein arm defect (43%), followed by inner dynein arm defect (23%), mixed inner and outer dynein arm defect (18%) and central apparatus defect (1%). Quality of sample is similar at nasal or tracheal level. However, it has to be free from recent infection to avoid secondary changes. Compound cilia and microtubules defects are typical secondary features. Inner dynein arm defect and radial spoke defect are also commonly seen after infective insult. Hence, a mandatory second sampling for analysis has to be performed 4–8 weeks after the last infection to avoid false positives.

Ciliary beat frequency Mucociliary beat frequency (CBF) and pattern (CBP) analysis by high-speed video technology under microscope help to pick up 15% PCD that have normal structure under TEM. Normal cilia beat forward and backward in the same plane without sideway sweep at a frequency of 12–14 Hz, while those with PCD beat at ~3 Hz or slower. Different ultra-structure defect can result in different beat pattern. Cilia with

outer dynein arm defects or mixed defects are virtually immotile with the occasional low-amplitude flickering motion. Those with inner dynein arm defect or radial spoke defects have a stiff beating movement with reduced amplitude and those with transposition defects beat at circular patterns. A normal mucociliary beat frequency and pattern makes PCD unlikely.

Cell culture Cell culture is a demanding and time consuming technique used to eliminate environmental influence on cilia structure and function. It is done by growing ciliated epithelial cells in an antibiotics-containing medium. The newly grown cilia, which are free from any secondary changes, are used for diagnostic tests like TEM, CBF and CBP analysis. Cell culture is mostly used in eliminating false positives due to chronic infection and to confirm less common phenotypes, like ciliary disorientation, ciliary aplasia, central microtubular agenesis and inner dynein arm defects.

MANAGEMENT

The aims of treatment are to prevent and treat pulmonary exacerbation so as to minimize lung damage, to control nonpulmonary symptoms and to promote normal growth and development. The management includes antibiotics, inhaled medications, anti-inflammatory medications, airway clearance, immunizations and fertility advice. Early diagnosis and implementation of a multi-disciplinary approach is associated with better outcome.

General measure including adequate up-to-date vaccination and environmental control to avoid pollutant, including cigarette smoke, should always be implemented. Nutritional support with calorie at 110–120% of that recommended for a normal population is required to support adequate normal growth in those symptomatic PCD.

Pulmonary Control

This is classified according to clinical features (**Table 1**). Pulmonary treatment (**Table 2**) includes measures to improve mucociliary clearance, to minimize lung damage due to infection and to decrease airway inflammation. Daily chest physiotherapy is essential for mucous removal. Exercise is encouraged because both taking deep breath and its bronchodilation effect help in mucous removal. Normotonic or hypertonic saline nebulizer is also helpful to clear sputum in our experience. DNase is useful in cystic fibrosis (CF), but case reports showed conflicting results

Table 1 Classification of control of PCD

Symptoms in the previous week	Controlled	Partly controlled	Uncontrolled
Cough	Little or no	Increased	> 3 features
Sputum volume and color	Little or no sputum	Increased volume or yellowish/greenish color	
Limitation of physical activities	None	Any	
Affect social life/daily activities	None	Any	
Emergency admission for pulmonary exacerbation	None	1 or 2/year	3 or more/year

Table 2 Stepwise approach to treatment of PCD

Basics	Step 1	Step 2	Step 3	Step 4
Aim to maintain lung function, decrease exacerbation and emergency admission Allow normal daily life				
← Step down if improving and step up if deteriorating →				
	5.85% NaCl solution nebulized for 10–15 minutes QD	5.85% NaCl solution nebulized for 10–15 minutes BD	5.85% NaCl solution nebulized for 10–15 minutes TDS	Multidisciplinary meeting to work out a tailor-made regime to arrest the deterioration
Education	Chest physiotherapy QD	Chest physiotherapy BD	Chest physiotherapy TDS	
Environmental control	Breathing exercise with resistor/vibrator, e.g., Acapella QD	Breathing exercise with resistor/vibrator, e.g., Acapella BD	Breathing exercise with resistor/vibrator, e.g., Acapella TDS	
Avoid pollutants exposure	*Bronchodilator (when necessary)	*Bronchodilator (when necessary)	*Trial of LABA + ICS (stop after 3 months if no benefit is demonstrated)	
Aerobic exercise			"Eradication and/or ^long-term cycled therapy with Neb and/or systemic antibiotic	
Immunization			Consider other measures to help airway clearance (i.e., CPAP, cough assist)	
Nutrition		#Antibiotic (2 weeks course)		

*Only in those with documented airway bronchodilator responsiveness.

#Sputum/induced sputum should be performed at least every 3 months, prescribe antibiotic according to latest sensitivity result; start with amoxicillin, if sputum showed commensals only/Co-amoxycyclavulanate, if the patient is at risk of aspiration.

"Eradication therapy for *Pseudomonas*: IV antipseudomonal antibiotics for 2 weeks ± colistin nebulization 75–150 mg (1–2 million units) BD for 2 weeks–3 months.

^ Long-term cycled therapy, usually start with 2–4 weeks of PO and/or Neb antibiotic, to be given every 3 months. Nebulized therapy: Gentamicin 80 mg BD or colistin (depending on bacterial culture and sensitivity).

^3 times per week azithromycin (10 mg/kg/dose) may help to reduce exacerbation and cough.

when used in PCD. Mucolytics are not useful while antitussive medication should be avoided.

Antibiotics Prompt and aggressive treatment of respiratory infection is the key to treatment. High dose oral antibiotics should be started at first sign of acute pulmonary exacerbation and it has been demonstrated to lead to improvement in lung function. Antibiotics choice should be guided by current or previous sputum culture result. If it is not available, oral Co-amoxycyclavulanate can be given empirically based on the fact that *Haemophilus influenzae*, *Staphylococcus aureus*, *Streptococcus pneumoniae* are the most common isolated organisms. Atypical *Mycobacterium* and *Pseudomonas species* tend to affect children of older age. Induced sputum for culture should be saved for surveillance every 3 months during acute exacerbation or when clinical response to treatment is suboptimal. Antibiotics choice should be changed according to sensitivity result. Prophylactic treatment is only considered in those experience recurrent pulmonary exacerbation and those with poor lung function. *Pseudomonas* infection (**Table 3**) should be treated with an aim to eradicate, while long-term antipseudomonal therapy should be given for chronically infected patients.

Anti-inflammatory treatment Case reports have demonstrated beneficial effects of macrolides in PCD. Azithromycin shows a good immunomodulatory effect, antisecretion effect with minimal side effect. Other anti-inflammatory medications like oral steroid and nonsteroidal anti-inflammatory drug are not recommended. Inhaled corticosteroids are not given routinely unless the patient is deteriorating. Clear outcome measures and success criteria need to be decided *a priori* to guide the continuation of inhaled corticosteroids beyond 3–6 months of trial.

Nonpulmonary Treatment

This includes daily nasal lavage with home-made or proprietary saline preparation (**Box 1**) and the authors found the 1.5% NaCl solution delivered by syringe with head-tilted to be highly effective and safe for the 1.5% NaCl solution. High dose antibiotics should be given for acute sinusitis. Acute otitis media should be treated with antibiotics while effusion should be managed conservatively with regular audiometry monitoring. Hearing aid may be considered if necessary, but grommet insertion should be avoided due to persistent otorrhea in 33% cases. Infertility can be managed by technology assisted fertility by intracytoplasmic injection of sperm or *in vitro* fertilization.

PROGNOSTIC FACTORS

Regular lung function monitoring is essential. Chest X-ray is easily accessible, but its sensitivity to early bronchiectasis is low. High resolution computer tomography (HRCT) is superior in this aspect but large radiation dose prohibit it from being used regularly. More than 50% children and 100% adults PCD patients have bronchiectasis. Delayed diagnosis, recurrent and severe infection are indicators for more extensive involvement. Middle and lower lobes of lung are more likely to be affected due to less effective mucus drainage by gravity. One-third of PCD patient have FEV₁ (forced expired volume in one second) less than 80% predicted at diagnosis. Those diagnosed late tends to have poorer lung function. With good adherence to treatment from expert centers for 10 years, 60% PCD patients' FEV₁ remain static, 10% show at least 10% improvement, but ~33% still deteriorate by more than 10%.

Table 3 Treatment for *Pseudomonas* infection

Step 1	First time isolation	Ciprofloxacin PO for 2 weeks
Step 2	Failed eradication with 1st line treatment	IV antipseudomonal antibiotics for 2 weeks OR Ciprofloxacin PO for 4 weeks + Colistin nebulization for 3 months OR Colistin nebulization for 3 months
Step 3	Long-term treatment for colonization	Gentamicin nebulization 80 mg BD OR Tobramycin nebulization 160 mg BD OR Colistin nebulization 1–2 MU BD

Abbreviation: po, per oral.

BOX 1 Methods of performing nasal lavage**Method 1 (Head-tilt)**

1. Tilt head to one side or lie on bed on the side
2. Breathe through the mouth. Avoid nasal breathing, talking or swallowing for the risk of aspiration
3. Push in irrigation fluid via one nostril (via nostril on upper side) and the fluid will exit from the other nostril or through the mouth
4. Repeat Step 3 with head tilted to the other side

Method 1**Method 2****Method 2 (Upright)**

1. Sit down with head up
2. Hold the breath
3. Push in irrigation fluid via one nostril and allow fluid to pass down the throat
4. Lean forward with head down and allow irrigation fluid to drip out from nostrils or split out from throat.

PREVENTION

Antenatal counseling of affected family and genetic investigation, if gene involved is known. Otherwise, there is no effective way to prevent PCD.

IN A NUTSHELL

1. Primary ciliary dyskinesia could be due to structural or functional defects of cilia.
2. Outer and inner dynein arm defect accounted for 80% of cases.
3. Nasal exhaled nitric oxide more than 150 ppb excludes PCD.
4. Rhinosinusitis, otitis media and persistent bacterial bronchitis are commonly found in PCD.
5. Bronchiectasis is identified in more than 50% children and 100% adult with PCD.
6. Around 33% of PCD patients had FEV₁ dropped by more than 10% in 10 years follow-up.
7. Early use of antibiotics for pulmonary exacerbation is essential to preserve lung functions.
8. Regular chest physiotherapy and inhalation of hypertonic saline are important to prevent exacerbation of bronchiectasis.

MORE ON THIS TOPIC

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Chapter 39.28

Cystic Fibrosis

SK Kabra, Kana Ram Jat, Rakesh Lodha

Cystic fibrosis (CF) is the most common life limiting recessive genetic disorder in Caucasians with an incidence of approximately 1 in 2,500 children born in the United Kingdom. It is less common in African Americans (1 in 15,000) and in Asian Americans (1:31,000). It also affects other ethnic groups such as black population with an incidence of 1 in 17,000 and the native American population with an approximate incidence of 1 in 80,000.

EPIDEMIOLOGY

Cystic fibrosis was thought to be extremely rare in India. Recent reviews suggest that CF does occur in Indian children. The incidence in migrant Indian populations in the USA has been estimated to be 1 in 40,000 while in UK it has been estimated 1 in between 10,000 and 12,000. The precise incidence of CF among Indians is unknown. Low level of suspicion and poor availability of facilities for diagnosis have delayed the diagnosis in our country. The median age of diagnosis among Indian Americans is 12 months compared with 6 months among Caucasian American children and reflects a low index of suspicion for the disease even among Indians in western countries. Delayed diagnosis of CF results in severe malnutrition which is one of the bad prognostic indicators for survival.

ETIOPATHOGENESIS

The basic defect in CF is a mutation in the gene for chloride conductance channel, i.e., cystic fibrosis transmembrane conductance regulator (CFTR) located on chromosome 7. The failure of chloride conductance by epithelial cells leads to dehydration of secretions that are too viscid and difficult to clear.

Till now more than 1,800 mutations in the gene have been recognized (www.genet.sickkids.on.ca). The most common mutation is delta F 508 which constitutes about 70% of the total cases. The frequency of this mutation in Indian children is reported to be between 19% and 44%. The proportion of children with delta F 508 mutations from other countries in Asia is less than that in the Caucasian population.

CLINICAL FEATURES

The clinical features of CF are variable and depend on age of diagnosis, supportive care and treatment received. The common clinical presentation includes meconium ileus in neonatal period, recurrent bronchiolitis in infancy and early childhood, recurrent lower respiratory tract infections, chronic lung disease, bronchiectasis, steatorrhea and with increasing age pancreatitis and azoospermia. Pancreatic insufficiency is present in more than 85% of CF patients (**Table 1**).

DIAGNOSIS

The diagnosis of CF should be suspected by the presence of a typical phenotype or family history and confirmed by the demonstration of a high sweat chloride (> 60 mEq/L) on two occasions and/or by identifying CF causing mutations on both the alleles of the child. Nasal potential difference measurements can be used as an alternative to sweat test but is not widely available.

In the absence of sweat chloride estimation and mutation analysis at most centers in India, CF may be suspected on presence of supportive investigations as given in **Flow chart 1**. Children with

Table 1 Common clinical features of cystic fibrosis

0–2 years	%
Steatorrhea	85
Failure to thrive	85
Rectal prolapse	20
Meconium ileus	10–15
Obstructive jaundice	15–20
Hypoproteinemia/anemia	15–20
Bleeding diathesis	15–20
Heat prostration /hyponatremia	15–20
Bronchitis/bronchiolitis	15–20
Staphylococcal pneumonia	15–20
2–12 years	
Malabsorption	85
Recurrent pneumonia	60
Nasal polyposis	6–36
Intussusception	1–5
> 12 years	
Clubbing	
Azoospermia	98
Chronic pulmonary disease	70
Portal hypertension	25
Abnormal GTT	20–30
Focal biliary cirrhosis	10–20
Gallstones	4–14
Diabetes mellitus	7

suspected CF may be treated with supportive care, but label of CF should be given after confirmation by sweat test or mutations.

DIFFERENTIAL DIAGNOSIS

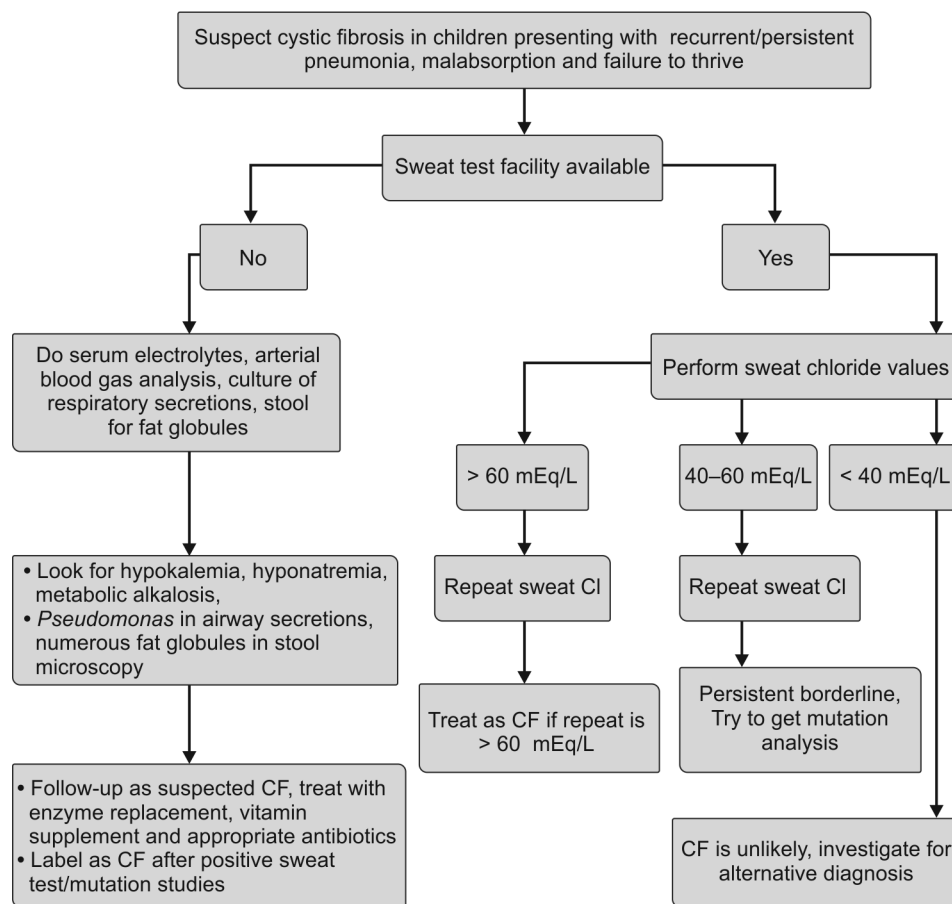
Children presenting with recurrent pneumonia and gastrointestinal infections (diarrhea) secondary to primary or secondary immune deficiency may closely mimic CF. Children with CF may have frequency of stool, that is large volume, foul smelling and greasy, while infective diarrhea produces watery or blood stained stools. Children with immune deficiency may have multisite recurrent infections due to usual as well as unusual microbial agents, while children with CF get predominantly GI and respiratory symptoms.

MANAGEMENT

The treatment of CF in children includes respiratory management; nutritional care; anticipation and early diagnosis of liver disease, diabetes and other organ dysfunction.

Respiratory Management

Lung damage in CF is caused by excessive poorly effective inflammatory processes in response to bacterial infection of normally sterile airways. Respiratory therapy aims to limit lung damage by decreasing the number of infecting organisms and suppressing the inflammatory process and hyper-reactivity of airways. The principle components of care used to achieve this include (a) airway clearance techniques, (b) antibiotics, and (c) anti-inflammatory agents.

Flow chart 1 Approach to diagnosis and management of cystic fibrosis

Airway Clearance Techniques

The airway secretions are viscid in CF. These are difficult to clear and lead to secondary infections and damage to respiratory tract. Airways can be kept clear by adequate hydration, chest physiotherapy, and judicious use of antibiotics and mucolytic agents. To keep the secretions less viscid, it is important to maintain good hydration by ensuring intake of plenty of liquids and extra salt.

Chest Physiotherapy

Chest physiotherapy techniques for keeping airways clean includes following methods: (i) Postural drainage and chest clapping; (ii) active cycles of breathing; (iii) positive expiratory pressures (PEP); (iv) high pressure PEP; (v) flutter therapy; (vi) autogenic drainage; and (vii) high frequency chest wall oscillation (HFCWO). The method can be selected for an individual on the basis of age of the patient, clinical status, experience of the physiotherapist, personal preference of patients, and social issues including level of support. For infants and young children, postural drainage and chest clapping may be more convenient. Cyclical breathing and autogenic drainage require patient's cooperation and can be used in older children. Flutter therapy, PEP, and HFCWO require special devices and training. They can be used under supervision of the physiotherapist.

Mucolytic Agents

Various mucolytic agents have been used by oral as well as inhalation route. N-acetylcysteine has propensity to cause bronchospasm, hemorrhagic tracheitis and impaired ciliary clearance, its use is limited to selected cases where other measures

fail to clear the air passage. Recombinant human DNase (rhDNase) has been found to reduce the viscoelasticity and adhesiveness of sputum in animal models. DNase, given as aerosol, increases mucociliary clearance and reduces incidence of respiratory infections; it also decreases rate of hospitalization, number of days missed from work or school and the frequency of CF related symptoms. The side effects of rhDNase are few and mild and include upper airway irritation (voice change, laryngitis, pharyngitis), rash, chest pain, and conjunctivitis. A small proportion of patients (2–4%) may develop antibodies to rhDNase. It is recommended in doses of 2.5 mg once or twice a day. But it is a rather expensive treatment with limited utility. There is no role of oral mucolytic drugs including bromhexine and ambroxol.

Antibiotic Therapy

The commonly encountered microbial agents causing pulmonary exacerbation in children with CF include *Staphylococcus aureus*, *Haemophilus influenzae b*, *Pseudomonas spp*, *Burkholderia cepacia*, etc. Different viruses, *Mycoplasma*, *Mycobacterium spp*, and *Aspergillus* are other important pathogens responsible for pulmonary exacerbation. It is important to select an antibiotic on basis of organisms isolated from respiratory secretions. Periodic cough swab cultures may help in empirical treatment of acute exacerbation.

The drugs effective against common pathogens and their doses are given in **Tables 2 and 3**. The duration of intravenous therapy is 2–4 weeks. An early identification of respiratory infection and administration of oral antibiotics may decrease the need for hospitalization and intravenous antibiotics. The early

Table 2 Organisms associated with exacerbation of pulmonary infection in patients with cystic fibrosis and appropriate intravenous antibiotic treatment

Prevalent bacteria	First choice		Alternative choice	
	Antibiotics	Dose	Antibiotics	Dose
<i>S. aureus</i>	Cefazolin	25–50 mg/kg every 6 hours	Vancomycin	15 mg/kg every 6 hours
<i>H. influenzae</i> and <i>S. aureus</i>	Ticarcillin clavulanate plus Gentamicin	100 mg of ticarcillin per kg and 3.3 mg of clavulanate/kg every 6 hours 3 mg/kg every 8 hours		
<i>S. aureus</i> and <i>P. aeruginosa</i>	Ticarcillin clavulanate Tobramycin plus gentamicin/amikacin	100 mg of ticarcillin per kg and 3.3 mg of clavulanate/kg every 6 hours 3 mg every 8 hours		
<i>P. aeruginosa</i> only	Ticarcillin plus tobramycin	100 mg/kg every 6 hours 15 mg/kg every 12 hours	Tobramycin plus ceftazidime, piperacillin or imipenem Aztreonam plus amikacin	3 mg/kg every 8 hours 50 mg/kg every 8 hours 100 mg/kg every 6 hours 15–25 mg/kg every 8 hours 50 mg/kg every 8 hours 5–7.5 mg/kg every 8 hours
<i>P. aeruginosa</i> and <i>Burkholderia cepacia</i>	Ceftazidime plus ciprofloxacin	50–75 mg/kg every 8 hours 15 mg/kg every 12 hours	Ceftazidime, plus Chloramphenicol or Trimethoprim – sulfamethoxazole	50–75 mg/kg every 8 hours 15–20 mg/kg every 8 hours 5 mg of trimethoprim/kg IV and 25 mg of sulfamethoxazole/kg every 6 hours
<i>B. cepacia</i> only	Chloramphenicol or Trimethoprim sulfamethoxazole or both	15–20 mg/kg every 6 hours 5 mg of trimethoprim/kg and 25 mg of sulfamethoxazole/kg every 6 hours		

Table 3 Oral antibiotics commonly used to suppress respiratory pathogens in patients with cystic fibrosis

Pathogen	Antibiotics	Doses
<i>S. aureus</i>	Cloxacillin	12.5 mg/kg every 6 hours
	Cephalexin	12.5 mg/kg every 6 hours
	Amoxicillin-clavulanate	10–15 mg of amoxicillin/kg and 2.5–3.75 mg of clavulanate/kg every 8 hours
	Erythromycin	15 mg/kg every 8 hours
	Clarithromycin	7.5 mg/kg every 12 hours
<i>H. influenzae</i>	Cefaclor	10–15 mg/kg every 8 hours
	Amoxicillin	10–20 mg/kg every 8 hours
<i>S. aureus</i> and <i>H. influenzae</i>	Cefixime	10 mg/kg/day
	Amoxicillin-clavulanate	10–15 mg of amoxicillin/kg and 2.5–3.75 mg of clavulanate/kg every 8 hours
	Trimethoprim – sulfamethoxazole	5 mg of trimethoprim/kg and 25 mg of sulfamethoxazole/kg every 12 hours
	Cefpodoxime	5 mg/kg every 12 hours
	Cefuroxime	20 mg/kg every 12 hours
<i>P. aeruginosa</i>	Ciprofloxacin	20–30 mg/kg/day in 2–3 divided doses
<i>B. cepacia</i>	Trimethoprim – sulfamethoxazole	5 mg of trimethoprim/kg and 25 mg of sulfamethoxazole/kg every 12 hours

indications of starting oral antibiotics include increase cough and expectoration, change in the color of expectoration, decrease in activity, impaired appetite, fever, and weight loss. Fever may not be a common clinical manifestation of acute exacerbation of infections. The treatment of acute exacerbation of infection, if the patient is known to be colonized with *Pseudomonas* includes

antibiotics effective against *Pseudomonas* (fluoroquinolones, ceftazidime, cefoperazone, piperacillin, imipenem or meropenem in combination with an aminoglycoside). If the colonization status is not known, then a combination of drugs effective against *Pseudomonas* and *Staphylococcus* are used empirically. The commonly used oral antibiotics include fluoroquinolones. These drugs may be started early and given for 2–3 weeks when acute exacerbation is suspected.

Aerosolized antibiotics The airways of CF patients get colonized with *Pseudomonas spp.* and may be responsible for frequent exacerbation. Complete eradication of *Pseudomonas* from airways of CF patient is extremely difficult. Use of aerosolized antibacterials has shown good results in treating patients who are chronically colonized with *Pseudomonas*. The drugs commonly used are tobramycin and colistin. These drugs can be given either daily or intermittent (one month alternating with 1 month off) till 1–2 cough swab cultures are negative for *Pseudomonas*. These can be started again when cultures are positive for *Pseudomonas*.

Bronchodilator and Inhalation Steroid Therapy

Bronchial hyper-responsiveness occurs in 25–50% patients particularly during intercurrent infections and in those with poor baseline lung function. Some patient may have atopic asthma as well as CF. Factors associated with atopic asthma include: exercise induced wheezing, persistent nocturnal coughing, cough or wheeze following exposure to allergens, concomitant eczema and/or rhinitis, and family history of asthma. These patients may benefit with bronchodilators and inhaled steroids and these may be used on a prolonged basis if there is a consistent response to these drugs.

Nutritional Management

Increase Caloric Intake

Many parents may restrict fat intake in diet of children with CF and it may improve their symptoms of malabsorption but at the cost of

poor growth. Parents should be encouraged to give balanced diet without restricting fat. The caloric need increases in situations with persistent chest infection or frequent pulmonary exacerbations. Caloric demand may increase up to 50% during acute pulmonary exacerbation.

Oral Caloric Supplements

In addition to caloric needs, supplementary feeds by using commercial preparations or home made feeds can be used. The caloric supplements are given in addition to the regular meals. For Indian children, caloric supplements can be given by using locally available food.

In some patients, short-term/long-term nasogastric or gastrostomy feeding is required. Indications for nasogastric feeding are (1) no weight gain for 6 months even with adequate caloric intake, (2) acute pulmonary exacerbation with poor oral intake, (3) consistently poor appetite and inability to maintain caloric intake, (4) before major surgical procedures, (5) during periods of increased caloric requirement, e.g., puberty and pregnancy.

The feeds may be home made liquid feeds or commercially available formulae. Pancreatic enzymes should always be given with supplementary feeds.

Supplementation of Fat-soluble Vitamins and Minerals

Children with pancreatic insufficiency are at risk of developing deficiency of fat-soluble vitamins. Recommended doses of vitamin A and D are given in **Table 4**. Recommended doses of vitamin E are 50 mg for children below 1 year of age, 100 mg for children between 1 year and 10 years and 200 mg thereafter. In children with clinical manifestation of vitamin K deficiency and those having liver disease, a dose of 10 mg vitamin K daily is recommended. All vitamins should be given with meals and enzyme. Deficiency of water-soluble vitamins is not common. Role of iron, zinc, and selenium supplements remains uncertain.

Salt loss in sweat is excessive in CF patients. Increased sweating in hot weather may result in clinical manifestations of hyponatremia. Sodium supplement is recommended in hot climate. There are no studies on the doses of daily salt for Indian children. Till data are available, we advise daily extra salt intake of 2.5 g in children below 10 kg, and 5 g in children above 10 kg weight.

Pancreatic Enzyme Supplement

Regular enzyme supplement in form of enteric-coated spherules has improved nutritional management significantly. The enzyme preparation is given with meals. The pancreatic supplements can be given in form of capsules or the spherules can be spread over small amount of food in a teaspoon. It is given just before food. The initial doses of enzyme can be 3,000 (1/3rd capsule)–10,000 IU (one capsule) per meal. Doses can be adjusted by observing stool consistency and weight gain in the child. The enzyme doses can be adjusted with monitoring of frequency and characteristics of stools, and weight gain. The enzyme dose should not exceed 10,000 IU of lipase/kg/day.

Table 4 Recommended doses of vitamin A and D in cystic fibrosis

Age	Recommended daily dose	
	Vitamin A	Vitamin D
Less than 6 weeks	2000 IU	200 IU
6 weeks to 6 months	4000 IU	400 IU
More than 6 months	8000 IU	800 IU

Management of GIT Manifestations

The common GI manifestations in CF include pain in abdomen, abdominal distention, meconium ileus equivalent, intussusception, and meconium peritonitis. Pain abdomen in CF may be due to pancreatic insufficiency, rectal prolapse, gastroesophageal reflux, or intestinal obstruction. Pain, abdominal distention, and rectal prolapse due to pancreatic insufficiency respond to increased doses of enzymes. For gastroesophageal reflux, prokinetic agents along with H-2 receptor antagonist are required. Pain in abdomen secondary to constipation can be treated with oral lactulose in doses of 1 mL/kg/day in two divided doses.

Management of meconium ileus during neonatal period and meconium ileus equivalent includes maintenance of fluid and electrolyte balance, administration of hyperosmolar solutions (Gastrografin) per orally or by enema and bowel washes in some patients. Meconium peritonitis and unresponsive meconium ileus may need surgical intervention.

Management of liver disease Ursodeoxycholic acid may prove to affect the natural history of cystic fibrosis-related liver disease. A regular monitoring of liver function test and imaging studies should be part of management.

Assessment and Monitoring

The assessment of illness and monitoring for progress of illness can be done by clinical examination and various laboratory tests. The assessment may be annual or continuous.

Various clinical scoring systems have been developed to provide both a numerical assessment of patient's status and a way of documenting progress in response to treatment.

Other monitoring include pulmonary function test, X-ray film of chest, chest CT scan, ultrasound abdomen, echocardiography, blood chemistry such as glucose, calcium, vitamin levels, transaminases levels, etc. Frequency of these tests depends on the severity of illness and age of patients.

Gene Therapy

Cystic fibrosis is caused by mutations of the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. Consequent to mutations in parental genes; airway epithelial cells have insufficient *CFTR* functions. As this can be corrected *in vitro* by transfer of the normal *CFTR* gene into airway epithelial cells, it is reasonable to hypothesize that the respiratory manifestations of CF could be prevented by transfer of the normal *CFTR* cDNA to airway epithelium *in vivo*. Studies on gene therapy have not yet produced any breakthrough.

CFTR Modulators

Research in biochemical manipulation to improve *CFTR* function is of great interest. In this direction, a great success has been documented with the use of medication ivacaftor (Kalydeco), that is a *CFTR* potentiator, and has improved *CFTR* function in patients with the G551D mutation, which represents about 4% of patients with CF. The medication is approved for use in children above 6 years of age with this mutation.

PROGNOSIS

The median life expectancy for CF is now over 30 years, and it is projected that in newborn infants it will become more than 40 years. There is increasing evidence of the advantages of newborn screening for CF and subsequent specialist care in high burden countries and races. Management concentrates on optimizing nutritional status and preventing lung infection and inflammation. Survival analysis of Indian children with CF suggest that early mortality was associated with early onset (below 2 months) of

symptoms, severe malnutrition at the time of diagnosis, more than four episodes of pulmonary exacerbations in a year and colonization with *Pseudomonas*.

MORE ON THIS TOPIC

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IN A NUTSHELL

1. Cystic fibrosis (CF) is an emerging disease in Indian children.
2. CF is autosomal recessively inherited illness. Gene is located on chromosome 7.
3. It is a multisystem illness, predominantly involving respiratory and GI systems during childhood.
4. Diagnosis is based on demonstration of sweat chloride value of more than 60 mEq/L with clinical symptoms.
5. Management consists of airway clearance, antibiotics for pulmonary exacerbations and pancreatic enzyme supplementation.

Chapter 39.29

Bronchiectasis

Lokesh Guglani

Bronchiectasis is a suppurative obstructive lung disorder characterized by thickening and dilatation of bronchial walls leading to persistent airway inflammation and mucus retention, and recurrent pulmonary infectious exacerbations; caused by a variety of pulmonary and systemic disorders. It is usually the end result of chronic obstruction and inflammation in the airways, and leads to persistent symptoms, reduced lung function and progressive damage to the lungs over time. Cystic fibrosis (CF) remains the most common cause of bronchiectasis among children in Europe, America and Australia, and has been discussed separately in Chapter 39.28. Primary ciliary dyskinesia (PCD) has been covered separately in Chapter 39.27. All causes other than CF are combined under the heading *non-CF bronchiectasis* and their assessment and management will be discussed in this chapter.

EPIDEMIOLOGY

Since the first description of suppurative phlegm in patients with bronchiectasis by René Laënnec (the inventor of the stethoscope) in early 19th century, the epidemiology of this condition has changed significantly. The introduction and widespread use of antibiotics and vaccines (specifically for pertussis and measles) throughout 20th century had a significant impact on its prevalence across all age groups. However, it is now being diagnosed relatively early in both developed and developing worlds, primarily due to increasing use of high resolution chest computed tomography (CT) scans. The natural history of bronchiectasis in children and its rate of progression over time are determined by the underlying cause, the extent of lung involvement, and the adherence to prescribed treatments. There are no data regarding cause-specific mortality rates in children, although the outcomes are better defined for CF bronchiectasis.

ETIOLOGY

The various conditions that are known to cause non-CF bronchiectasis are listed in **Box 1**.

PATHOGENESIS

Cole's vicious cycle model explains the pathogenesis of bronchiectasis over time (**Fig. 1**). In the setting of any of the underlying risk factors, the presence of neutrophilic inflammation releases proteases that cause damage to the elastic tissue and smooth muscles in the walls of the airways over time. These alterations of the airway anatomy cause thickening and dilatation of the distal bronchi and bronchioles, leading to retention of mucus and poor clearance of airway secretions. This microenvironment of inflamed respiratory epithelium and excessive mucus allows bacterial proliferation, which over time leads to the colonization of airways with various pathogens. A wide variety of pathogens such as *Staphylococcus*, *Streptococcus*, *Pneumococcus*, *Haemophilus influenzae*, various anaerobic, and microaerophilic bacteria and *Pseudomonas aeruginosa* can be found in the bronchiectatic airways. With repeated infectious exacerbations over time, the damage to the airway walls becomes more extensive, leading to further impairment of mucus clearance, thus perpetuating the vicious cycle of infection → inflammation → mucus retention → infection, over and over again.

Reid categorized the pathologic changes in the airways into cylindrical, saccular/cystic and varicose bronchiectasis (**Table 1**)

BOX 1 Causes of non-CF bronchiectasis in children

1. **Airway Injury:** Tuberculosis, recurrent pneumonia, chronic aspiration, bronchiolitis obliterans (postinfectious or post-transplant), nontuberculous mycobacterial infections
2. **Airway obstruction or anomalies:**
 - **Extrinsic compression:** Vascular ring, tumors, lymphadenopathy
 - **Intraluminal obstruction:** Foreign body impaction, granulation tissue, endobronchial masses (carcinoid, broncholithiasis)
 - **Airway stenosis or malacia**
 - **Airway cartilage/connective tissue disorders:** Mounier-Kuhn syndrome (congenital tracheobronchomegaly), Williams-Campbell syndrome (cartilage deficiency), Marfan syndrome
3. **Impaired airway clearance:** PCD, cystic fibrosis, poor airway clearance secondary to neuromuscular disorders
4. **Immunologic abnormalities:**
 - **Primary immune deficiencies:** Immunoglobulin deficiency, Job syndrome
 - **Acquired immune deficiencies:** HIV infection, post-transplant immunosuppression
5. **Chronic inflammatory disorders:** Inflammatory bowel disease (Crohn disease, ulcerative colitis), autoimmune disorders (rheumatoid arthritis, Sjögren syndrome), allergic bronchopulmonary aspergillosis
6. **Miscellaneous:** Graft-versus-host disease, $\alpha 1$ -antitrypsin deficiency, yellow nail syndrome, Young's syndrome, postradiation fibrosis
7. **Idiopathic.**

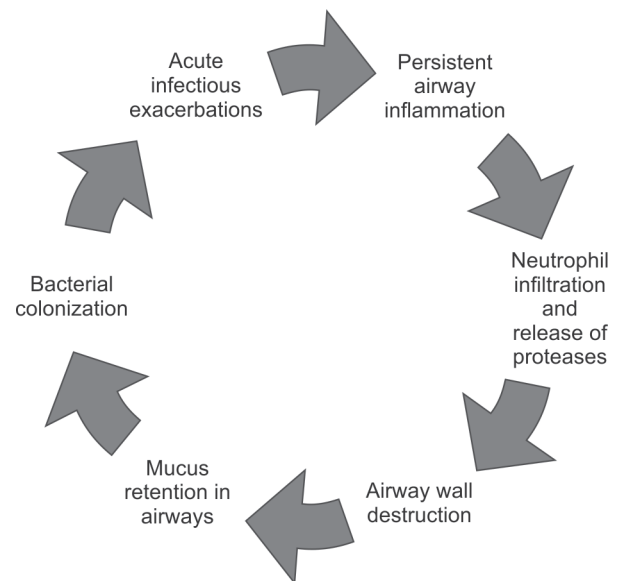


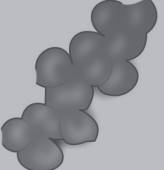



Figure 1 Cole's vicious cycle model to explain the pathogenesis of bronchiectasis

based on the lung histopathologic findings. *Tubular or cylindrical bronchiectasis* represents dilated airways that can sometimes also be seen in patients with pneumonia, but may show some improvement over time. *Saccular or cystic bronchiectasis* occurs with further worsening dilatation of the airways that shows airway segments with large cystic dilatations or saccules, sometimes giving the appearance of a cluster of grapes. *Varicose bronchiectasis* has (just like varicose veins) focal areas of constrictions along a dilated airway that may be due to defects in the bronchial wall.

The initial origin of bronchiectasis can be either focal obstruction (either due to extrinsic compression or intraluminal mass/lesion) involving a specific region or lobe of the lung; or it may be diffuse, in relation to a chronic sinopulmonary condition

Table 1 Pathologic changes in the airways of subjects with bronchiectasis

Categories	Airway changes
	 <p>Normal</p>
Cylindrical	 <p>Cylindrical</p> <p>Dilated bronchi with well defined, straight outlines (tram track appearance, signet ring appearance)</p>
Saccular or cystic	 <p>Cystic</p> <p>Bronchial segments with ballooned appearance (sometimes showing air fluid levels), can appear as clusters of large thick walled cysts (honeycombing)</p>
Varicose	 <p>Varicose</p> <p>Bronchi with alternating areas of dilatation and constriction, giving it a beaded appearance</p>

(such as PCD). The impairment of mucociliary clearance combined with increased mucus production (secondary to hypertrophy of submucosal glands, and metaplasia of goblet cells down into the bronchioles) leads to mucus build up, chronic wet cough, and bacterial colonization. Neutrophils predominate in the airway walls and release proteases and other inflammatory cytokines that cause continued airway inflammation and perpetuation of the vicious cycle of obstruction → infection → inflammation.

CLINICAL FEATURES

Most children with bronchiectasis have a history of persistent, wet cough that may be associated with expectoration of purulent sputum in older children. They may also present with an infectious exacerbation that may sometimes be triggered by a viral infection, with fever, increased cough chest pain and shortness of breath. Presence of chronic sinusitis may indicate ciliary dysfunction, cystic fibrosis or primary immunodeficiency. It is also important to evaluate patients for ongoing aspiration, especially if they have underlying neurologic conditions or congenital anomalies. Presence of an airway foreign body can also lead to repeated infections leading to the development of bronchiectasis over time. Children with bronchiectasis may have increased anteroposterior diameter of the chest due to air trapping as a result of coexistent small airway disease, and may also show digital clubbing. Lung auscultation may reveal localized crackles or rhonchi over the area of involvement in most cases, but wheezing tends to be less common. In general, the progression of bronchiectasis over time may cause patients to develop exercise intolerance and shortness of breath with activity. They may also develop significant failure to thrive and may have chronic hypoxemia requiring supplemental oxygen as their lung involvement becomes more extensive. Hemoptysis may occur due

to erosion of the inflamed airway walls that are in close proximity with pulmonary vessels, but is generally less common in children.

DIFFERENTIAL DIAGNOSIS

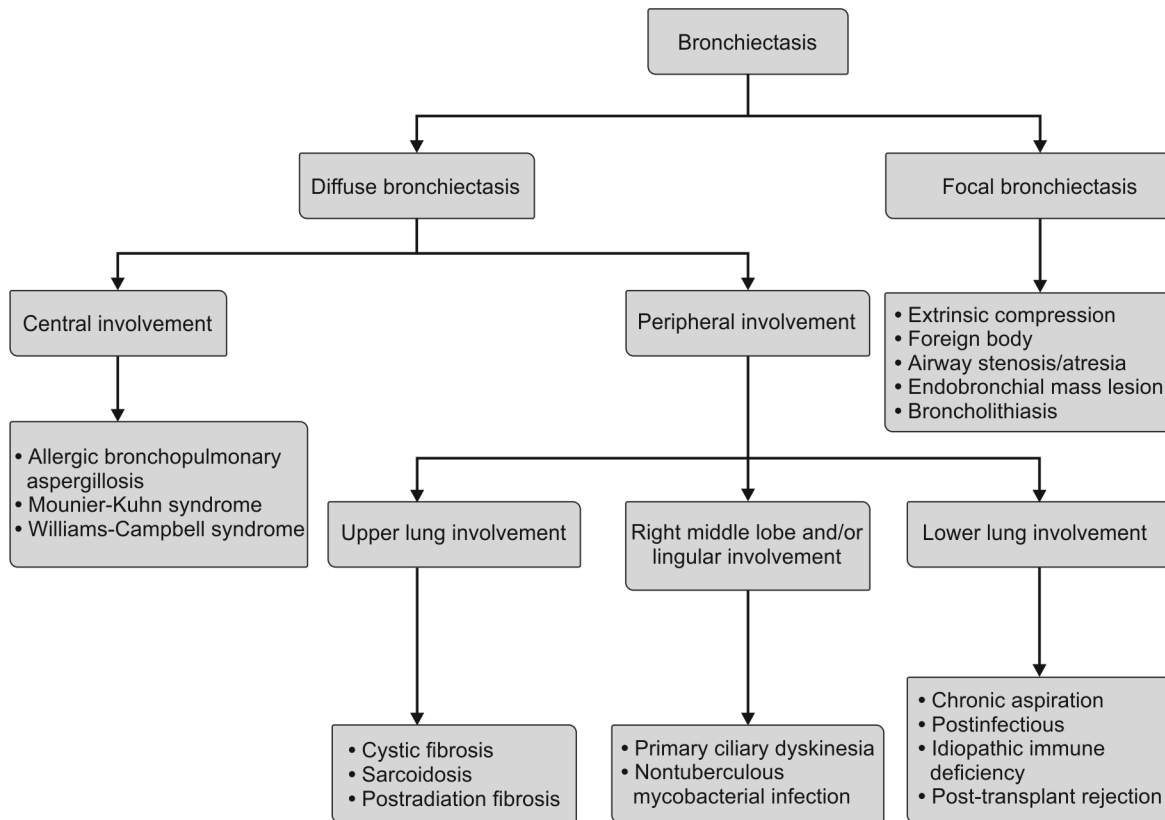
Bronchiectasis should be clinically suspected in children with history of recurrent pneumonias, failure to thrive or chronic wet cough. Since it is a pathologic diagnosis, the underlying cause can be narrowed down from the list of causes in **Box 1**, based on each individual patient's profile and to some extent from the location of the bronchiectatic changes on imaging. **Flow chart 1** shows the patterns of involvement seen on chest CT scan and the associated causes/conditions that are commonly encountered.

Approach to Diagnosis

The diagnostic work-up is directed toward confirming the diagnosis of bronchiectasis, assessing its severity and finally, to confirm its etiology in order to help initiate appropriate therapies. Prior history of specific infections such as tuberculosis or whooping cough in early childhood may lead to postinfectious bronchiectasis. The initial evaluation with a chest X-ray can show dilated thickened airway walls (seen as tram-track lines or ring-shaped shadows for end-on bronchi) but some milder cases may be missed. Other additional abnormalities such as dilated trachea (Mounier-Kuhn syndrome) or persistent atelectasis in one lobe (foreign body or airway compression/mass) may require further testing.

High resolution chest CT is more sensitive as it takes images through 1–1.5 mm slices for every 10 mm of the lung and can better define the extent of lung involvement in bronchiectasis. Airway dilatation can be assessed more objectively, if the airway diameter is noted to be 1.5 times greater than the diameter of the accompanying blood vessel (the *signet ring sign*). Other features such as lack of tapering of the dilated airways as they extend into the periphery of the lung; thickened bronchial walls with extensive mucus plugging; and significant air trapping are additional findings. Localized areas of dilatation of multiple airways within a single lobe can sometimes give the appearance of cystic bronchiectasis. Attention should be paid to other structures such as hilar or mediastinal lymph nodes, vascular anatomy, or congenital airway abnormalities. If the dilated airways can be seen extending up to 1 cm under the pleural surface, it suggests significant dilatation. Some of these early changes (especially those seen in cylindrical bronchiectasis) may be seen in patients with pneumonia and may be reversible after appropriate therapy. Hence, CT imaging should preferably be done after the patient has fully recovered from recent illness.

Initial laboratory evaluation for patients with bronchiectasis should include respiratory cultures to identify specific pathogens (for bacterial, tuberculosis or nontuberculosis mycobacteria and fungal etiologies); tuberculin skin test; sweat test to rule out cystic fibrosis; and basic immunologic work-up (quantitative immunoglobulin levels, antibody responses to diphtheria/tetanus and pneumococcal serotypes). Additional testing may be indicated for patients with suspected chronic aspiration that may be undertaken with modified barium swallow study, videofluoroscopic swallow study, or nuclear scintigraphy. For patients with localized abnormalities on imaging or those who are unable to expectorate sputum, a flexible fiberoptic bronchoscopy should be performed to assess airway anatomy, rule out localized airways obstruction (foreign body, airway anomalies, intraluminal mass lesions or extrinsic airway compression) and to obtain a bronchoalveolar lavage specimen for cultures. A nasal ciliary biopsy may be performed for patients with situs inversus, recurrent sinusitis or otitis media to evaluate for PCD. It is important to remember that the classic triad of Kartagener syndrome (situs inversus, chronic sinusitis and bronchiectasis) is seen in 50% of

Flow chart 1 Patterns of involvement of various etiologies in bronchiectasis

PCD patients. Pulmonary function testing should be performed to assess lung function at baseline, to track response to therapy and monitor changes in lung function over time. Generally, patients with bronchiectasis show an obstructive pattern with low Forced Expiratory Volume in one second (FEV_1) and/or FEV_1 /Force Vital Capacity (FVC) ratio, but some patients with more advanced lung disease may show a mixed obstructive and restrictive defect (latter primarily due to fibrotic changes). For patients with specific features, genetic testing for conditions such as Cystic Fibrosis (steatorrhea, failure to thrive) or PCD (situs in versus, recurrent sinusitis or otitis media) may be considered, if initial screening tests (sweat test or nasal ciliary biopsy) are positive or equivocal.

MANAGEMENT

Once bronchiectasis has been diagnosed, therapies are initiated to prevent further progression of damage to the airway walls, to control symptoms and minimize infectious exacerbations. The long-term management of bronchiectasis includes the following components:

- Airway clearance techniques to aid the removal of excessive airway secretions
- Inhaled mucolytics to enhance the removal of secretions
- Antibiotics
- Anti-inflammatory medications
- Immunization and general protective strategies.

Airway Clearance Techniques

Airway clearance therapies can be individualized based on patient's age, preference and availability of equipment. Manual chest percussive therapy with cupped hands for younger patients or huff-cough techniques for older patients can help to mobilize the secretions. Use of handheld devices such as Acapella, Flutter, Lung

Flute or Quake is based on their ability to transmit vibrations down the airways and loosen up the secretions. High frequency chest wall oscillation device (or Chest Vest) has been used in CF patients, but can also be useful for patients with non-CF bronchiectasis.

Inhaled Mucolytics

Inhaled mucolytic medications such as 7.2% hypertonic saline have been used. Use of recombinant human DNase (Pulmozyme®) has not been shown to be effective for patients with non-CF bronchiectasis. Use of inhaled bronchodilators may be helpful for patients with significant airway reactivity.

Antibiotics

Antibiotic therapy for acute exacerbations can be determined based on the pattern of airway colonization for each patient. Sputum may be difficult to obtain in younger children, but induced sputum techniques or use of throat swabs from posterior pharynx can be useful in guiding antibiotic selection. Even without culture results, treatment can be started (with amoxicillin-clavulanic acid, or with second or third generation cephalosporins) to cover the most common pathogens seen in the airways of patients with bronchiectasis. For outpatient therapy, these antibiotics should be prescribed for at least 10–14 days, but if there is failure to respond to oral antibiotics or a severe acute illness, then intravenous antibiotics may become necessary. As the airways of patients with bronchiectasis become colonized with specific pathogens over time, they may require chronic therapy to prevent acute exacerbations or further worsening of lung function. Like CF patients, many non-CF bronchiectasis patients also get colonized with *Pseudomonas aeruginosa* and may benefit from long-term use of inhaled antibiotics (inhaled tobramycin, aztreonam) to suppress the growth of *Pseudomonas* in their airways.

Anti-inflammatory Drugs

Anti-inflammatory therapies that have been utilized in patients with bronchiectasis include oral azithromycin (administered 3 times a week) and high-dose ibuprofen. Data for their effectiveness is mostly extrapolated from CF literature, and there are no direct studies in children with non-CF bronchiectasis. Inhaled corticosteroids may have a limited role as anti-inflammatory agents in non-CF bronchiectasis, and should be prescribed if a patient has comorbid reversible bronchospasm as well.

Supportive Management

Finally, adequate immunization should be ensured for all children with bronchiectasis and they should continue to receive yearly influenza vaccination. Children above 24 months of age should also receive a booster dose of 23-valent pneumococcal vaccine to keep them protected against pneumococcal pneumonias. Those with underlying immune deficiency should not be given live viral vaccines.

Prevention of exposure to cigarette smoke and other inhaled irritants, avoiding contact with individuals with a cold or respiratory infection, and adequate nutritional rehabilitation are general preventive strategies that can help to improve the quality of life of patients with non-CF bronchiectasis. A specialist should periodically evaluate children with non-CF bronchiectasis and if possible, their lung function and nutritional status should be tracked over time to monitor response to therapies and to assess the natural history of their disease. Oxygen supplementation may become necessary for patients with more advanced disease once they develop chronic hypoxemia due to severe ventilation-perfusion mismatch. Surgical resection of involved lung lobes may be considered for patients with focal bronchiectasis, especially if they continue to have failure to thrive, severe infections, or recurrent hemoptysis despite optimal medical therapies. Patients with diffuse lung involvement, whose bronchiectasis has progressed to severe end-stage lung disease ($FEV_1 < 15\%$), may require bilateral lung transplantation as a last resort treatment option.

PROGNOSIS

The outcomes for patients with non-CF bronchiectasis generally depend on the nature of the underlying disease process, the age of onset, the rapidity of progression of airway wall changes and patient's adherence to prescribed therapies.

PREVENTION

Prompt evaluation of chronic wet cough, treatment of respiratory infections with appropriate antibiotics, nutritional rehabilitation,

and provision of adequate immunization coverage can be helpful in preventing the onset and progression of lung disease in most patients with bronchiectasis.

IN A NUTSHELL

1. Bronchiectasis is a suppurative obstructive lung disorder that is characterized by thickening and dilatation of bronchial walls that leads to persistent airway inflammation and mucus retention, recurrent pulmonary infectious exacerbations and may be caused by a variety of pulmonary and systemic disorders.
2. Its pathogenesis is explained by Cole's vicious cycle model that describes how repeated infections or airways obstruction can cause continued airway inflammation and obstruction, which leads to repeated infections, that further perpetuates the inflammation.
3. Besides a detailed history and examination, high resolution chest CT scans are helpful in definitive assessment of severity and possible underlying cause of non-CF bronchiectasis.
4. Therapy with antibiotics, airway clearance techniques, mucolytics can help to prevent the progression of lung damage.
5. Outcomes for patients with non-CF bronchiectasis generally depend on the nature of the underlying disease process, the age of onset, the rapidity of progression of airway wall changes and patient's adherence to prescribed therapies.

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Chapter 39.30

Lung Abscess

Kana Ram Jat, Meghna Sharma

A lung abscess is a localized central necrosis and suppuration of the lung parenchyma following microbial infection leading to formation of single or multiple cavities containing fluid and necrotic material.

EPIDEMIOLOGY

The incidence of lung abscess in children is 0.7 per 100,000 admissions per year and it is less common than adults. Advances in the field of antibiotics have drastically reduced the incidence of lung abscesses. Mortality secondary to lung abscess has also reduced and now mostly occurs in malnourished, debilitated and immunocompromised children.

CLASSIFICATION

Lung abscesses can be classified based upon the duration and etiology. *Acute lung abscess* is less than 6 weeks in duration and *chronic* is more than 6 weeks of duration. Lung abscess can also be categorized into primary and secondary. *Primary lung abscesses* are those that develop in previously healthy children, whereas *secondary lung abscesses* develop in a child with predisposing factors such as cystic fibrosis, gastroesophageal reflux, congenital thoracic malformations, airway obstruction, postoperative complications of tonsillectomy, bronchiectasis, tracheoesophageal fistula, septicemia (septic emboli), spread from extrapulmonary site (mediastinum and diaphragm), immunodeficiency or aspiration secondary to neurological illness. A primary lung abscess is almost always solitary and mostly on right side, whereas secondary abscess can be solitary or multiple and may dominate on left side. An abscess may also develop as infection or complication of pre-existing bulla or lung cyst.

ETIOLOGY

Most of the lung abscesses are polymicrobial. Anaerobic and aerobic bacteria are the main causative organisms but in rare cases, especially in immunocompromised children, parasitic and fungi have also been implicated. The aerobic bacteria causing abscess are *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Haemophilus influenzae*, *Actinomyces* and *Nocardia* species, *Mycobacterium* and gram-negative bacilli. Anaerobes are those mostly found in oral cavity like *Peptostreptococcus*, *Bacteroids*, *Fusobacterium* and microaerophilic *Streptococcus*. Nonbacterial pathogens causing lung abscess include *Paragonimus*, *Entamoeba* species and fungus like *Aspergillus*, *Cryptococcus*, *Histoplasma* and *Candida*.

PATHOGENESIS

Lung abscess begins as small areas of necrosis in a consolidation which join to form a big cavity containing necrotic debris surrounded by a thick wall of infected and inflammatory tissue. Sometimes this process may establish communication with an airway and cause partial expectoration of purulent content and a resultant air-fluid level. Lung abscess may develop in any part of the lung, but aspiration related abscess most commonly affects the dependent areas. In recumbent position right upper lobe, left

lower lobe and apical segment of both lower lobes are dependent areas. Right side is more affected than left side because of vertical bronchus. As the aspirate reaches lower airways, bacteria present in the aspirate initiate an infection which if not cleared by host defense mechanism cause pneumonitis, ultimately leading to tissue necrosis after 1 or 2 weeks. Rarely septic emboli from septic thrombophlebitis or tricuspid valve endocarditis may also lodge in the lung. Hematogenous seeding of bacteria in lung can also occur in septicemia. Histopathologically, lung abscess is a suppurative focus surrounded by fibrous tissue and mononuclear infiltration.

CLINICAL FEATURES

Clinical features are often subacute and include low grade fever, cough, sputum production, hemoptysis, anorexia, weight loss, and night sweats. Symptoms may last for few weeks before diagnosis. However, a smaller proportion of cases may present with high grade fever, respiratory distress and chest pain. Sputum may present only in big children which may or may not be foul smelling. Signs include toxic looking child, febrile, clubbing, and respiratory distress. Chest findings are decreased breath sounds, dullness on percussion, and bronchial breath sounds which can be amphoric or cavernous.

COMPLICATIONS

Acute complications are empyema formation following rupture in pleural space, pneumothorax, massive hemoptysis and respiratory failure. Other complications may include bronchopleural fistula and fibrosis of involved lung.

DIFFERENTIAL DIAGNOSIS

Lung abscess may be difficult to diagnose if associated with empyema or consolidation. Pneumatoceles, bullae or lung cyst may also lead to diagnostic confusion. An infected lung cyst may also simulate an abscess, but can usually be differentiated by thin wall of the cyst (between 1 mm and 4 mm) and no signs of inflammation. Pneumatoceles again are thin walled air-filled cyst that develops in lung parenchyma which may occur due to bacterial infection, most commonly *Staphylococcus aureus* or barotraumas. Congenital pulmonary airway malformation (CPAM), a condition caused by overgrowth of abnormal lung tissue that may form fluid filled cysts or result in the failure of the development of the tiny air sacs, may sometimes look like an abscess. Cavitary lesions can also be present in Wegener's granulomatosis, a form of vasculitis affecting small and medium vessels, but it will have other systemic manifestations also.

DIAGNOSIS

Radiology forms the mainstay of diagnosis of lung abscess. Chest X-ray characteristically shows a well circumscribed thick wall cavity with air fluid levels (**Fig. 1**). Diagnosis of lung abscess is difficult on chest X-ray if it is accompanied by empyema, consolidation or pneumatoceles. In such cases contrast-enhanced computed tomography (CECT) chest makes a definitive diagnosis and also helps differentiate between a loculated empyema, sequestration, necrotizing pneumonia, pneumatocele and congenital thoracic malformation from a lung abscess. Lung abscess looks like a radiolucent lesion with irregular and well defined thick margins that makes an acute angle with pleural chest wall (*egg on the carpet* appearance), whereas loculated empyema forms an obtuse angle with chest wall (*egg under the carpet* appearance). Pneumatoceles are characterized by localized air collection that has thin and smooth wall with or without air-fluid level. Ultrasonography

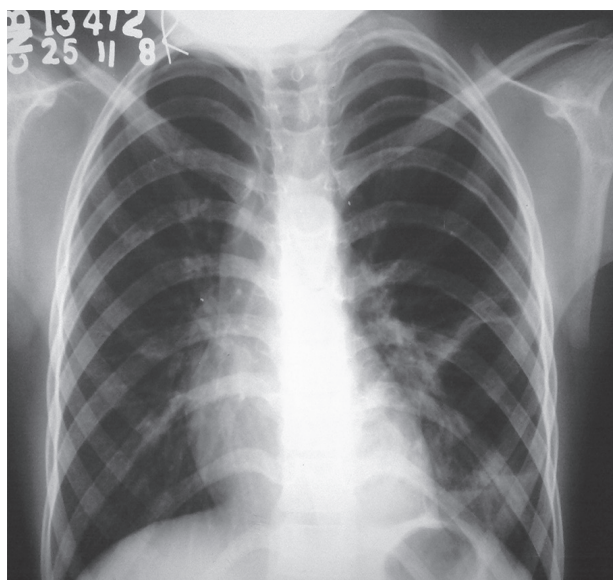


Figure 1 Lung abscess in the left lower lobe

(USG) may detect peripheral lung abscess with pleural contact or one associated with a consolidation. Detection of etiologic agent, although difficult, may be helpful to curtail empiric therapy in lung abscess. Infected hydatid cyst and tuberculosis should be ruled out in all patients.

TREATMENT

Antibiotics form the mainstay of treatment for lung abscess. Empirical antibiotic therapy is usually needed as most of the time abscess material may not be available for examination. Most useful empiric therapy for lung abscess should include drugs for both aerobics and anaerobes. The usual regimen is combination of penicillin and clindamycin. Clindamycin is preferred over metronidazole for anaerobic coverage as it has good intracellular uptake and is stable in low pH and produces excellent results. Metronidazole has failed to produce desired results despite of good anaerobic spectrum. Alternative drugs include amoxicillin with clavulanic acid, piperacillin with tazobactam, cefoxitin, or imipenem. If culture of sputum, blood or aspirated pus comes positive, then antibiotics should be modified accordingly. Parenteral antibiotic therapy should be continued for 2–3 weeks. It should be followed by oral antibiotic to complete a total duration of 6–8 weeks. Postural drainage should be done in all patients

where ever possible. In most cases, antibiotic therapy along with postural drainage is sufficient for cure of lung abscess. Patients, who are not responding to this therapy in 7–10 days, may require abscess drainage through thoracotomy, thoracoscopy or CT guided percutaneous aspiration. Lobectomy should be reserved for patients with severe abscess which fail to respond clinically and radiologically to above treatment. Massive hemoptysis, although rare in children, is another indication of surgery.

PROGNOSIS

Overall, the prognosis of primary lung abscess is good and most patients respond well to antibiotic therapy and only few patients require surgery. For secondary lung abscess, prognosis is determined by underlying predisposing condition.

IN A NUTSHELL

1. Lung abscess is less common in children as compared to adults.
2. *Staphylococcus aureus* is the main causative organism; anaerobes are also responsible in many cases.
3. Radiology is the mainstay for diagnosis of lung abscess.
4. Most of children with lung abscess require conservative treatment with antibiotics for 6–8 weeks. Penicillin plus clindamycin is the empirical therapy, to begin with.
5. Prognosis of primary lung abscess is very good, but prognosis of secondary lung abscess depends on underlying predisposing condition.

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Chapter 39.31

Tracheobronchial Foreign Body Aspiration

Varinder Singh, Ankit Parakh

Tracheobronchial foreign body (TFB) aspiration is a common problem in childhood which requires quick diagnosis and management. TFB in children can present with varying manifestations ranging from acute life-threatening airway obstruction to a persistent atelectasis and localized bronchiectasis. Diagnosis and retrieval of foreign body from airways requires a bronchoscopy. Rigid bronchoscopy has been the main diagnostic and therapeutic procedure for children suspected to have a TFB, although recent literature suggests that flexible bronchoscope can be used for both purposes.

LOCATION OF FOREIGN BODY

The most common site of lodgment of TFB are the main bronchi; right main bronchus (30%) and the left main bronchus (30%), followed by the trachea (25%). Unusually TFB can be found in the bronchus intermedius, right lower lobe bronchi and left lower lobe bronchi. Since both the main bronchi are almost at the same angle at the carina in young children, TFB can lodge in either bronchi with equal rates unlike adults where the right main bronchus is shorter and straighter compared to the left. The clinical manifestation also depends on location of foreign body.

TYPES OF FOREIGN BODY

The aspirated TFB can be categorized broadly as *organic* and *inorganic*. Organic foreign bodies such as nuts and seeds are the most common type in children constituting around 80% cases. Peanut are the most common followed by gram seed, betel nut, pea nut kernel in India. Inorganic foreign bodies include plastic foreign bodies like whistles, pen cap, small parts of toys and metallic foreign body like metallic screws, nut bolts, and coins. Organic foreign bodies produce more inflammatory reaction, especially with seed, since they produce a chemical resin which can worsen the obstruction. While inert inorganic material may remain asymptomatic for long time; some sharp objects may lead to trauma to airways or various air leak syndromes.

CLINICAL SPECTRUM

Tracheobronchial foreign body aspiration is more common in younger children with almost 75% being less than 3 years of age. Young children have a higher propensity to aspirate foreign body because of oral exploration; lack of molar teeth, and poor swallowing coordination. Boys are more vulnerable and account for 65–70% of TFB aspirations. The exact reason behind male predominance is unclear. With the increasing use of head covers and scarves in the Islamic nations, aspiration of scarf pin is on the rise among young adult girls as they often hold this pin in their mouth while tying the head gear and thus risk aspiration.

The *most common symptom* is acute onset of cough, usually in the absence of any other sign of upper respiratory tract infection, and is present in more than 90% children. History of choking is a predominant feature of TFB aspiration and found in 70–80%. Presence of choking has a very high prediction for the presence of TFB, although the absence of choking does not rule out the

possibility of TFB body aspiration. Often choking accidents go unnoticed as the child may be alone or with other young children while aspirating and thus the event goes unreported. Such cases can present early if there is respiratory compromise or else present late with suppurative complications. Fever might be present in a few cases. Other important history includes acute onset respiratory distress, stridor, audible wheezing, and cyanosis. The history of change in voice should also be carefully elicited since it would indicate the presence of a laryngeal foreign body.

Clinical examination Respiratory examination would reveal stridor or a monophonic wheeze (might be unilateral in cases of a TFB in the bronchus, bilateral in cases of tracheal TFB). There would be reduced air entry on the side of the lodgment of the TFB (in cases of tracheal TFB air entry would be equal on both sides). The classical clinical triad of cough, wheezing, and decreased air entry has shown to have a low sensitivity (25–40%), but high specificity (95%) in some studies. In younger children, the aspirated TFB is often too large to enter the bronchial tree beyond carina and stays in the trachea. Such children will have no localizing feature.

Laryngeal foreign body would present with stridor with change in voice without any wheezing and reduced air entry. Tracheal foreign body can present as variable degree of respiratory distress, stridor, or acute life-threatening obstruction, but would have a monophonic wheeze and equal air entry. Foreign body in bronchial tree often presents as cough, unilateral decreased breath sounds, and wheezing. It should be remembered that TFB can be mobile and can cause variable signs with the movement of the TFB.

COMPLICATIONS

Acute complications include hypoxia and air leak syndromes (pneumothorax, hydropneumothorax, pneumomediastinum, and subcutaneous emphysema). Mortality has been well described in children with TFB aspiration. Forgotten TFB can lead to various long-term complications like recurrent unilobar pneumonia, persistent atelectasis, bronchiectasis, and bronchial stenosis.

RADIOLOGICAL DIAGNOSIS

Chest radiographs would usually be carried out in most patients with suspected TFB aspiration. Radiopaque TFB like pins, screws, etc., can easily be picked up by radiological examination but are uncommon. The most common TFB among children are not visualized directly on chest skiagrams as they are not radiopaque. However, nearly two-thirds of the cases have indirect evidence in form of overinflation of a lung or its part, or else atelectasis of a lung or its part. The indirect radiological findings of localized hyperinflation are secondary to a *ball valve phenomenon* and the atelectasis results from complete resorption of air after airway occlusion. Lung infiltrates and consolidation or air leak syndromes like pneumothorax, pneumomediastinum and subcutaneous emphysema can also be seen. Normal chest radiographs cannot exclude TFB as tracheal TFB may not produce any radiological change. Other radiographic techniques include radiographs in inspiration and expiration with the expiratory film showing air trapping, but it misses about a third or more of the cases. Fluoroscopy has also been described; would show similar findings of expiratory air trapping and reduced diaphragmatic excursion of the involved side.

There has been recent interest in multidetector computed tomography (MDCT) chest and virtual bronchoscopy for non-invasive diagnosis of TFB in children. Virtual bronchoscopy is a relatively new, noninvasive diagnostic method that gives a 3-dimensional view of the internal walls of the tracheobronchial tree through the reconstruction of axial images. The drawbacks

include radiation exposure, cost and nonavailability of the expertise. The sensitivity is not enough to recommend this at present. In the authors opinion the modality has been poorly useful and usually delays referral.

MANAGEMENT

Management of aspirated TFB depends on the location of TFB and the condition of the child. In children presenting with life-threatening TFB, basic life support (BLS) and pediatric advanced life support (PALS) guidelines should be followed. Immediate treatment of TFB by parents or caretakers may dislodge the foreign body. In infants, back slaps in a head down position with or without chest thrusts are the treatment of choice. Abdominal thrusts including the Heimlich maneuver appear more appropriate for older children.

Removal of the foreign body is the primary objective and mainstay of treatment. Rigid bronchoscopy has been the main diagnostic and therapeutic procedure for children suspected to have a TFB. Fiberoptic bronchoscopy (FOB) has been increasingly used for diagnostic purposes especially because of the high rates of negative rigid bronchoscopies. Some authors have suggested performing rigid bronchoscopies only in cases of asphyxiating TFB, radiopaque TFB and in children with clinical/radiological lateralizing signs; while in all other situations FOB is preferred. This approach will lead to best utilization of the two approaches as those with high probability of TFB undergo rigid scopy, where the extraction shall be possible at the same sitting.

Traditionally, rigid bronchoscopy under general anesthesia by the ENT surgeon is the procedure of choice for retrieving the TFB in children. Rigid bronchoscopes have the advantage of a wide working channel that permits good ventilation and control of the airway. It also acts as a conduit through which the foreign body can be removed. The availability of wide range of sizes of rigid bronchoscopes, superb optical telescopes for visualization, and the large array of ancillary instruments to retrieve TFBs has made it the favorite instrument in the management of pediatric TFB.

Pediatric flexible bronchoscope has been used, but has not gained popularity for extraction of TFB in children. Main drawbacks cited are the lack of ability to control the airway, small caliber of the suction channel and lack of ancillary instruments available to grasp the TFB. In recent years, flexible bronchoscopy has gained the popularity among respiratory endoscopist as a first choice for retrieval of foreign bodies in the children especially with availability of urological wire baskets. Flexible bronchoscopy can be performed under sedation with local anesthesia, can reach TFB lodged in distal airway and can obtain alternate diagnosis and take samples for bronchoalveolar lavage.

PREVENTION

Majority of the TFBs in children are organic food particles and lead to acute airway obstruction. Parents need to be educated regarding the factors leading to TFB aspiration in young kids like absence of moor teeth and poor swallowing coordination. There is also a need to create public awareness regarding the avoidance of nuts and various fruits with seeds in children less than 4 years. It should also be emphasized that toys should be appropriate for age and small

toy parts are a leading type of inorganic TFB. Other small objects like pen caps and so on should be kept out of reach of preschool children. Since most of the deaths secondary to TFB aspiration occur in home only, parents should be educated regarding the urgency of the condition and immediate hospitalization needs. Teaching BLS algorithms and especially Heimlich maneuver to the parents and community might reduce the chances of fatal accidents.

IN A NUTSHELL

1. Tracheal foreign body in children can present with varying manifestations ranging from acute life-threatening airway obstruction to a persistent atelectasis and localized bronchiectasis.
2. The most common site of lodgment of TFB is the main bronchi; right main bronchus; the left main bronchus, followed by the trachea.
3. The aspirated TFB can be categorized broadly as *organic* and *inorganic*.
4. The *most common symptom* is acute onset of cough, usually in the absence of any other sign of upper respiratory tract infection. A history of choking is mostly available.
5. Acute complications include hypoxia and air leak syndromes.
6. Nearly two-thirds of the cases have indirect radiological evidence in form of overinflation or atelectasis of a lung or its part. The indirect radiological findings of localized hyperinflation are secondary to a *ball valve phenomenon* and the atelectasis results from complete resorption of air after airway occlusion.
7. Diagnosis and retrieval of foreign body from airways requires a bronchoscopy. Rigid bronchoscopy has been the main diagnostic and therapeutic procedure for children suspected to have a TFB, although recent literature suggests that flexible bronchoscope can also be used for both purposes.

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Chapter 39.32

Central Hypoventilation

Mahesh Babu Ramamurthy, Daniel YT Goh

Respiration is regulated to maintain oxygen, carbon dioxide, and acid-base balance within a narrow range. The homeostatic mechanism involves a myriad of complex pathways and mediators, controlled largely by the central respiratory center in the brainstem in coordination with peripheral receptors and effectors.

DEFINITION

Central alveolar ventilation is diagnosed when the PCO_2 is more than 45 mm Hg due to decreased ventilatory drive. This can be either *congenital* or *acquired* (e.g., due to drugs or central nervous system diseases like cerebrovascular accidents, trauma and neoplasms). Congenital central hypoventilation may be primary, e.g., congenital central hypoventilation syndrome (CCHS) or secondary, e.g., due to Arnold-Chiari malformation.

CLINICAL SPECTRUM

The spectrum of central hypoventilation syndromes discussed here includes: (1) CCHS, (2) Rapid onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (ROHHAD), (3) Chiari malformation, and (4) Others: Prader-Willi Syndrome, familial dysautonomia, achondroplasia, and Leigh's disease. Central hypoventilation disorders are rare and often complex disorders that may involve alterations in mechanisms of ventilatory control and autonomic dysfunction.

CONGENITAL CENTRAL HYPOVENTILATION SYNDROME

Congenital central hypoventilation syndrome, also called Ondine curse, is a rare and severe form of central hypoventilation with autonomic nervous system dysregulation.

Etiology

A mutation in the *PHOX2B* gene (a gene that codes for a transcription factor that regulates neural crest cell migration and the development of the autonomic nervous system) is seen in more than 95% of children with CCHS. Over 90% of *PHOX2B* mutations in CCHS have an increased polyalanine repeat expansion mutation (PARM). There is a good correlation between increasing severity of disease and the number of PARMs. The remaining 10% have a nonpolyalanine repeat expansion mutation (NPARM) such as missense, nonsense, or frame shift. Certain PARMs have an autosomal dominant inheritance with incomplete penetrance. No structural central nervous system lesion is accountable for the manifestations of this syndrome have been confirmed.

Pathophysiology

The affected individuals have a lifelong impairment of arousal response to hypercarbia and hypoxemia and lack the perception of asphyxia. They lack ventilatory responsiveness to hypercarbia and hypoxia, both during wakefulness and sleep. Hypoventilation can occur both while awake and asleep in severe cases, while milder cases occur only during sleep. Gas-exchange disturbances occur predominantly during nonrapid eye movement (REM) sleep, in contrast to other sleep-related breathing disorders that are predominant in REM sleep.

Epidemiology

Congenital central hypoventilation syndrome is probably not as rare as the previous estimated prevalence of 1 case in 200,000 live births. It has been reported that nearly 1,000 children worldwide have *PHOX2B* mutation-confirmed congenital central hypoventilation syndrome.

There is no apparent racial or gender differences in occurrence. The children usually present at birth, but the diagnosis can be delayed because of variations in disease severity and a fluctuating course. Late-onset CCHS tends to present, following an infection or some other respiratory insult.

Clinical Features

The wide spectrum of clinical manifestation is related to the severity of the disorder. Infants can present with apnea at birth and many require mechanical ventilation. But some may mature and develop a pattern of breathing during wakefulness over time while apnea or central hypoventilation may persist during sleep. Symptoms of hypoventilation are more pronounced during even minor respiratory tract infections since, they do not mount respiratory responses to increased demands and they do not manifest signs like tachypnea and nasal flaring. Others may present at a later age, while some may present more subtly with right heart failure (cor pulmonale) as the first indication of CCHS. Still, others may present with unexplained apnea or an apparent life-threatening event or some may even die and be categorized as having sudden infant death syndrome (SIDS).

Associated Abnormalities

Patients may also have disorders of autonomic nervous system control, with increased frequency of cardiac arrhythmias (primarily sinus bradycardia and transient asystole), abnormalities in blood pressure, and pupil diameter control. About 15–20% of patients with CCHS also have Hirschsprung disease. Neuroblastoma may be present in about 5% of patients with CCHS. Ocular findings (abnormal pupils, abnormal irides or strabismus) can be found in up to 70% of cases.

Diagnosis and Evaluation

The diagnosis of CCHS should be kept in mind in all children presenting with hypoventilation, with no neuromuscular, cardiac or pulmonary causes. A high index of suspicion is required to make this diagnosis. A positive diagnosis of CCHS is made by:

- Careful observation of respiratory pattern and gas exchange during both wakefulness and sleep. Hypoventilation with absent or negligible ventilatory sensitivity to hypercarbia and absent or variable ventilatory sensitivity to hypoxemia is a characteristic feature.
- Testing should ideally include all aspects of routine polysomnography including electroencephalogram (EEG), respiratory effort, oronasal airflow, ECG, saturations and end-tidal CO_2 monitoring. Where polysomnography is not available, continuous 24 hour monitoring of saturations along with repeated PCO_2 measurements with an indwelling arterial line is recommended.
- Mutation analysis for *PHOX2B* mutation is required to confirm the diagnosis of CCHS.

Investigations

The following tests are useful to exclude other etiologies for hypoventilation and gas exchange abnormalities:

- Cardiac evaluation including EEG and echocardiogram.
- Pulmonary evaluation including a chest X-ray, diaphragm fluoroscopy and/or ultrasound looking at diaphragmatic paralysis or paresis.

- If there is significant hypotonia, electromyography (EMG), nerve conduction velocity (NCV) and muscle biopsy may be useful to exclude neuromuscular diseases.
- MRI of the brainstem is useful to look at brainstem lesions that can cause similar clinical picture.
- Metabolic screen including urinary amino acids and organic acids can be useful.

Management

Congenital central hypoventilation syndrome is a lifelong condition and hence, a multidisciplinary approach will provide holistic care on a long-term for these children. The main goal of treatment for CCHS is to ensure adequate gas exchange both during sleep and wakefulness. Maintaining normal gas exchange throughout 24 hours will help in reducing the risks of cor pulmonale and neurological insult from chronic hypoxia. A genotype-phenotype correlation has been shown, with increasing respiratory support required with increasing number of PRAMs. Various studies have shown that about 6–33% of children with CCHS will require ventilatory support. Since this is a life-long condition which does not improve with time, these children will require some form of assisted ventilation in the home setting in the longer term. Oxygen administration alone will improve SpO₂ levels and reduce cyanosis, but will not prevent hypercarbia and its complications. Respiratory stimulants including theophylline and dexamphetamine have not been shown to improve the ventilatory drive in this population. Ventilatory support is adjusted to maintain saturations about 95% and low normal CO₂ levels between 30 and 40 mm Hg. Very close supervision by caregivers is required 24 hours a day.

Chronic Ventilatory Support

Portable positive pressure ventilator via tracheostomy This is the most reliable and effective method, and is safe. A pressure limited ventilation is used for efficient and safe ventilation.

Bilevel positive airway pressure (BiPAP) via nasal or facemask It allows ventilation without tracheostomy, but usually limited to children above 7 years of age who require only nocturnal support.

Negative pressure ventilation It is limited by lack of portability, skin irritation and a sense of feeling chilled, hence is not preferred.

Diaphragm pacing This mode of ventilation involves electrical stimulation of the phrenic nerve that results in diaphragmatic contraction. It requires surgical implantation of bilateral phrenic nerve electrodes and a subcutaneous sensor. An external pulse generator will then dictate the respiratory rate. This makes the system very portable. Children who require 24 hour support will benefit from diaphragm pacing during the day and positive pressure ventilator at night.

Identifying and treating other associated autonomic dysfunctions including Hirschsprung disease is an integral part of management.

Long-term Prognosis

Central hypoventilation during sleep is a life-long problem. Recurrent hypoxemic episodes contribute to morbidity and complications. The main causes of death include cor pulmonale, pneumonia and aspiration. Aggressive early diagnosis and prompt institution of ventilator support improves prognosis. A disturbance of cardiac autonomic regulation in CCHS may cause sudden cardiac death and indicate the need for a cardiac pacemaker. These children will require intensive home monitoring with additional care givers and monitoring equipment. Prevention of hypoxia reduces neurological sequel and cognitive disabilities.

RAPID ONSET OBESITY WITH HYPOTHALAMIC DYSFUNCTION, HYPOVENTILATION AND AUTONOMIC DYSREGULATION (ROHHAD)

This newly defined entity is different from late onset CCHS and is negative for *PHOXB* mutations. These children typically present between the age of 1.5 and 9 years with rapid onset obesity followed by signs and symptoms of hypothalamic dysfunction including water imbalance, temperature imbalance and behavioral abnormalities. The typical presentation of hypoventilation occurs after a viral infection, with symptoms of obstructive sleep apnea and alveolar hypoventilation. Nearly half of these children will experience a cardiorespiratory arrest. Currently, ROHHAD remains a clinical diagnosis and there is no genetic testing available.

PRADER-WILLI SYNDROME

Prader-Willi syndrome (PWS) is a genetic disorder with uniparental disomy. Its features include hypotonia, developmental delay, hypogonadism, marked hyperphagia, with consequent morbid obesity and psychological problems. Temper tantrums, emotional lability, obsessive symptoms, and cognitive impairment are seen in adolescence. Daytime hypersomnolence, nocturnal sleep disturbance, obstructive sleep apnea, nocturnal hypoventilation and reduced ventilatory response to hypoxia and hypercapnia are seen in PWS.

IN A NUTSHELL

1. Central alveolar ventilation is diagnosed when the PCO₂ is more than 45 mm Hg due to decreased ventilatory drive. It can be congenital or acquired.
2. Congenital hypoventilation can be either primary (CCHS) or secondary (Chiari malformation).
3. A diagnosis of primary congenital central hypoventilation syndrome (CCHS) should be considered in all children with evidence of hypoventilation without underlying cardiopulmonary, metabolic, neuromuscular or brainstem dysfunction. These children do not manifest signs of respiratory distress such as tachypnea and nasal flaring in response to hypoxia or hypercapnia.
4. Genotype data can help in diagnosis and prognosis of children with CCHS. Genetic testing should be performed for the *PHOX2B* gene.
5. The goal of management of patients with CCHS is to provide adequate ventilation to prevent long-term morbidities such as developmental delay and pulmonary hypertension.
6. Newer modes of ventilatory support such as noninvasive ventilation and diaphragmatic pacing prevent the need for tracheostomy and therefore improve quality of life for selected children.

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Section 40 CARDIOVASCULAR DISORDERS

Section Editors S Srinivasan, M Zulfikar Ahamed

Chapter 40.1 Historical Aspects and Advances in Pediatric Cardiology

S Srinivasan

On behalf of millions of neonates born with simple to complex congenital heart diseases and children with acquired heart diseases but yet lucky to survive and their courageous and supportive parents, it is expected of a pediatrician to place on record in this textbook the valuable contributions in terms of commitment, compassion, concern, courage to fight against all odds, dedication, efforts, faith, foresight, innovations, sacrifice, team spirit of pioneers and trendsetters in this field which brought about revolutionary changes in diagnosis and treatment. The future will focus in gaining more understanding of genetics and molecular biology involved and in maintaining the blend of enthusiasm, scholarship, skill, coordinated team spirit and above all humanism that have always been a hallmark of the advances made over 3 centuries.

"There is nothing more difficult to take in hand, more perilous to conduct, nor uncertain in its success, than to take the lead in the introduction of a new order of things, for the innovator has for enemies all of those who have done well under the old, and lukewarm defenders in all of those who may do well under the new."

Niccoló Machiavelli (1469–1527)

THE HISTORY

The first description of a congenital heart defect was given in 1673 by Steno of Denmark which in 1888, later named by Fallot of Marseilles as tetralogy of Fallot. This paved the way for affected children who would have otherwise not lived to see another day to become fully functional adults. The remarkable advances in pediatric cardiology started after a gap of another 45 years with the publication of a painstaking and monumental work of Maude Abbott *Atlas of Congenital Cardiac Disease* in 1936. This marked

the beginning of a major era of progress in understanding the pathophysiological anatomy of diverse congenital heart defects in still births, abortion and live neonates and surviving infants beyond 1 month.

The second era of progress highlighted the need for team approach between clinicians, physiologists interested in cardio-respiratory hemodynamics and electrophysiology, radiologists and daring surgeons including those involved in animal experimental surgery and beginning of era of open cardiac surgery. This resulted in the performance of Blalock-Thomas-Taussig anastomosis to save a child with tetralogy of Fallot from John Hopkins University of Baltimore in 1944.

The third era beginning in the mid-1970s with evolving extrinsic and intrinsic cardiac repair strategies based on concurrent progress in understanding of cardiovascular anatomy, cardiac electrophysiology, echocardiographic imaging techniques and the introduction of prostaglandin therapy in maintaining the ductal patency. This era also saw the decline in the incidence of rheumatic fever and rheumatic heart diseases in children, mostly in the developed world.

The early 1990s marked the beginning of the new era of progress in cardiac development in unraveling the mysteries of genetic, molecular and teratological basis of fetal cardiac malformations and working out possible preventive strategies in the occurrence of CHDs.

The reported mortality rates following intracardiac repair of complex congenital heart defects are currently less than 4–6%. Stroke and transient and often reversible neurocognitive postperfusion *pumphead* cardiopulmonary bypass complications are seen in 2–3% of these operated children.

Table 1 summarizes the development and advances in the management of congenital heart diseases and the achievers who made it possible. In developing countries with resource constraints and where the majority of the population lives in rural areas without proper access to tertiary care centers, the availability of surgical cure has been limited. In India, there is a rapid growth discernible in the development of therapeutic and surgical facilities in big cities both in private and governmental tertiary health sectors. Increased intake of trainees both in pediatric cardiology and cardiac surgery is helping to bring out well-trained workforce to take care of these children with correctible cardiac malformations.

Table 1 History of epoch making developments in pediatric cardiovascular surgery

Year	Advance in surgical intervention	Innovative pioneers
1938	Successful ligation of PDA; era of surgery for CHD	Robert E Gross (Children's Hospital in Boston)
1944	First successful repair of coarctation of the aorta in a 12-year-old boy	Crafoord and Nylin-Stockholm, Sweden
1945	End-to-end anastomosis between the SCA and PA as palliative shunt in tetralogy of Fallot	Taussig-Blalock-Vivien Thomas (Johns Hopkins, Baltimore, USA)
1945	Closed pulmonary valvotomy	Brock
1946	Potts shunt (descending aorta to left pulmonary artery)	WJ Potts Children's Memorial Hospital, Chicago

Contd...

Year	Advance in surgical intervention	Innovative pioneers
1947	Closed pulmonary valvotomy	TH Sellors, London
1948	Closed surgical creation of atrial septal defect	A Blalock and CR Hanlon Johns Hopkins Hospital
1948	Closed mitral commissurotomy	CP Bailey, Philadelphia
1949	Closed infundibulectomy (right ventricle)	RC Brock, London
1950	Atrial septectomy with Vivien Thomas' clamp for TGA palliation	Blalock, Hanlon and Vivien
1951	Pulmonary artery banding	WH Muller, JF Dammann Jr University of California, Los Angeles
1952	Open closure of ASD with aid of atrial well	RE Gross, Children's Hospital, Boston
1952	Open closure of atrial septal defect with aid of moderate hypothermia	FJ Lewis, University of Minnesota
1952	Ball valve in descending aorta for aortic regurgitation	CA Hufnagel Georgetown University, Washington DC
1952	Open pulmonary valvotomy with aid of right heart bypass	FD Dodrill Detroit
1953	Open closure of atrial septal defect with aid of heart-lung machine	JH Gibbon Jr. Philadelphia
1954	Open closure of ventricular septal defect with aid of cross-circulation	CW Lillehei University of Minnesota
1955	First series of open heart surgery with heart-lung machine	JW Kirklin Mayo Clinic
1956	Total repair of TOF in a 4-year-old girl. Artificial aortic valve implantation in late 1960s with an exceptionally low operative mortality	1 Nelson, Salt Lake City Utah, USA
1957	Corrective repair of TGA with interatrial baffle procedure and implantation of first human implantable pace maker	Ake Senning of Karolinska Institute—Sweden
1957	Coarctation of aorta: an <i>isthmus-plastic</i> patch aortoplasty (prosthetic patch introduction)	Vosschulte
1958	SVC to PA shunt (Glenn shunt)	WWL Glenn, Yale University
1958	Senning operation for TGA	A Senning, Stockholm
1960	Aortic valve replacement with ball valve	D Harken, Boston
1960	Mitral valve replacement with ball valve	A Starr, Portland, Oregon
1966	Repair of coarctation of subclavian flap aortoplasty	Waldhausen and Nahrwold
1963	Mustard operation for transposition of great arteries	William T Mustard Hospital for sick children, Toronto
1967	Aorta-coronary saphenous vein bypass	RG Favaloro Cleveland clinic
1967	Human heart transplantation	CN Barnard Capetown, South Africa
1968	Multivessel coronary artery bypass graft	WD Johnson Milwaukee
1968	Internal mammary artery-coronary graft	GE Green New York
1968	Fontan procedure	F Fontan Bordeaux, France
1975	Arterial switch for transposition of great arteries	AD Jatene Sao Paulo
1979–1981	WI Norwood procedure for hypoplastic left heart syndrome	Norwood Boston Children's Hospital
1982	Total artificial heart implantation	WC DeVries Salt Lake City, Utah
1984	Infant (8-month) heart transplantation	DA Cooley Texas Heart Institute, Houston
1985	Neonatal (4-day) heart transplantation	L Bailey Loma Linda University, California

Abbreviations: PDA, patent ductus arteriosus; CHD, congenital heart defects; SCA, subclavian artery; PA, pulmonary artery; TGA, transposition of great arteries; TOF, tetralogy of Fallot; ASD, atrial septal defect; SVC, superior vena cava.

Chapter 40.2

Development of the Heart

S Srinivasan

The rapid embryonic growth and the consequent nutrient requirements necessitate early development of a functional heart and vascular system. The cardiovascular system in fetus becomes functional by day 21 (end of third week).

ANGIOGENESIS AND PRIMITIVE HEART TUBE

Day 18–22

Proliferation and coalescing of angioblastic endocardial cell clusters result in the formation of blood islands and capillaries in the mesoderm on either side of the neural crest of the germ disc. Blood vessels are derived from the angioblasts arising from: (1) splanchnic and chorionic mesoderm and (2) mesenchyme in the yolk sac and umbilical cord. Two pairs of blood vessel cords are thus formed by these capillaries joining together; one pair running longitudinally at the lateral embryonic edge and the other pair running medially on either side of the neural tube and joining at their cranial end. The subsequent canalization of these two cords results in two endothelial heart tubes (**Figs 1A to C**).

Pericardium

Cardiac progenitor cells after migrating to the cardiogenic area (a region anterior to the prechordal plate or head region) start proliferating from the epiblast through the lateral streak to the lateral splanchnic plate mesoderm layer; they differentiate into

cardiac myoblasts. The intraembryonic cavity over it subsequently develops into the pericardial cavity.

Myocardium and Endocardium

Simultaneously between 22 days and 28 days, a thin inner endothelial lining is formed in this fused primitive heart tube. Proliferation of splanchnic mesocardium into the pericardial celom occurs to form the primordial myocardium. A gelatinous jelly like material rich in hyaluronic acid secreted by the thick myocardium insinuates in between the endothelial tube and cardiac jelly to develop soon after into primitive atrioventricular (AV) septum and valves. The inner visceral pericardium, the epicardium, is contributed by the mesothelial cells. The heart is now suspended in the cavity by blood vessels at both ends.

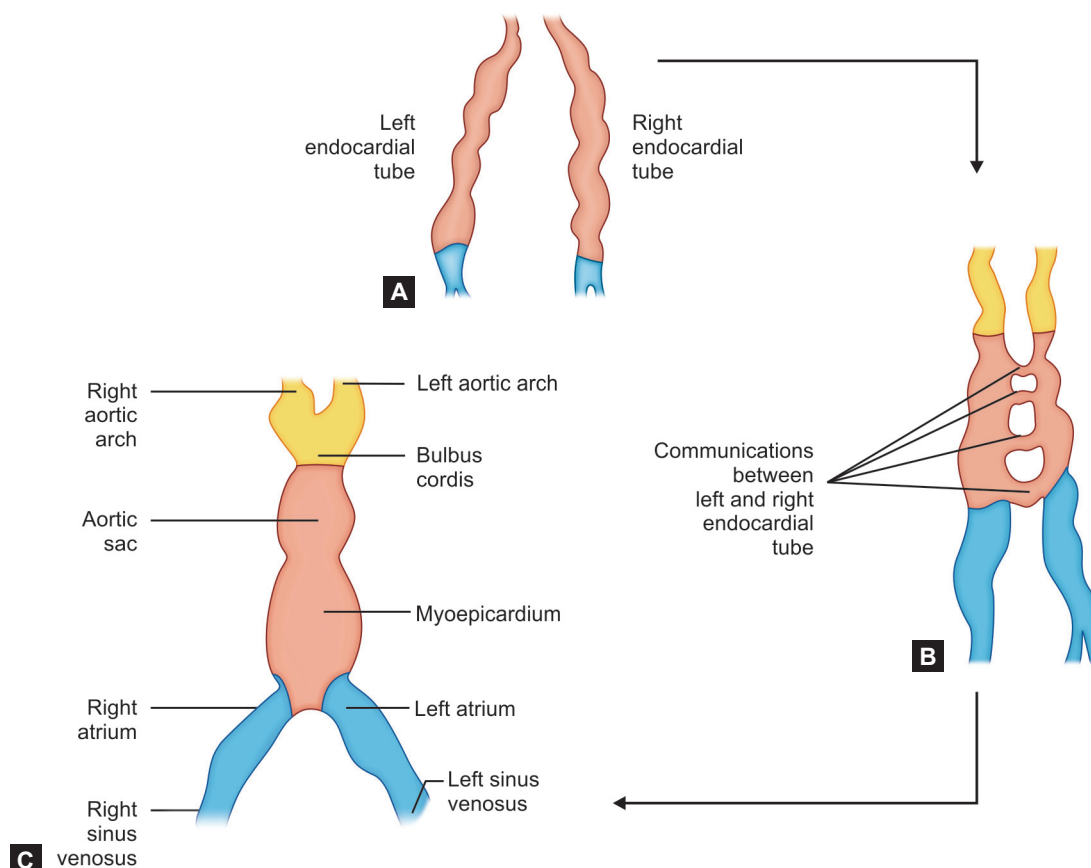
Heart Tube

The lateral folding and meeting of the lateral edges of the germ disc makes the embryo to assume a tubular shape and this in turn brings the two outer tubes to come together and fuse with each other craniocaudally forming a single primitive heart tube. Though the heart starts its beats from 22nd day, the blood circulation starts only between 27 days and 29 days.

Formation of Dorsal Aortae

Blood vessels formed on either side of the midline of the embryonic plate form other clusters of proliferating and coalescing mesodermal angiogenic cells dilate as vascular sacs. These canalized sacs join to form two longitudinal dorsal aortae. Aortic arches are formed and connect these two aortae with the primitive heart tube.

Figure 2 shows main subdivisions of heart tube and their fate.



Figures 1A to C Formation of blood vessels

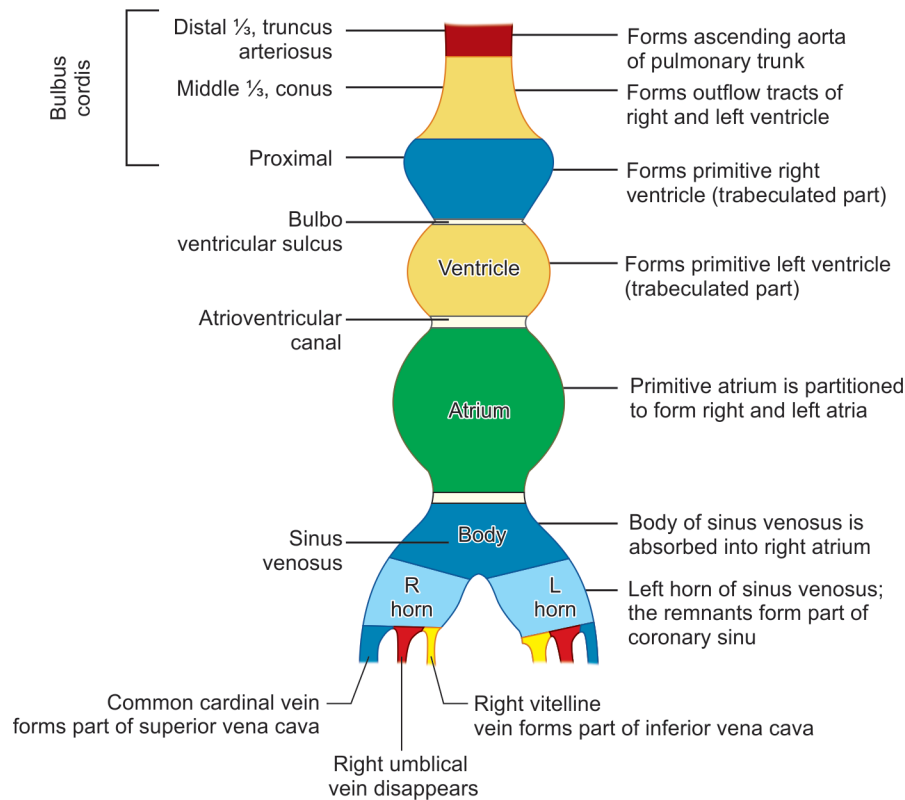


Figure 2 Main subdivisions of heart tube and their fate

FORMATION OF CARDIAC LOOP

23–28 Days

Atrioventricular Canal

The heart tube develops localized expansions throughout its length. Progressive elongation, alternate constrictions and dilatations of the fused primitive heart tube result in the formation of: (1) truncus arteriosus, (2) bulbus cordis, (3) primitive ventricle, (4) primitive atrium and (5) sinus venosus craniocaudally. Genetically programmed cardiac looping starts from twenty-third day and gets completed by twenty-eighth day, a major event in the development of the heart. Further elongation of the heart tube with faster growth of both bulbus and ventricle within this enclosed cavity results in bending of the cephalic portion. Initially an S-shaped tube and later a U-shaped heart tube is formed with this ventrally, caudally and rightward bending of the cephalic portion. Because of this bulboventricular loop formation, the atrium and sinus venosus tend to come dorsal to the bulbus and ventricle. The paired atrial zone seen outside the pericardial cavity develops into a common atrium and gets internalized inside the pericardial cavity. The narrowed area of the AV junction is the atrioventricular canal (AVC). Homeobox genes regulate the looping and proper organization of the heart segments.

Outflow Tracts

Bulbus cordis is relatively narrow except in its proximal third, where it becomes progressively trabeculated to form the right ventricle. The mid conus cordis gives rise to the outflow paths of both ventricles. The distal third is the truncus arteriosus which establishes continuity at its cranial end with aortic sac with its developing pair of aortic arches and pharyngeal arches—right and

left. It later gets partitioned to form the roots and proximal portions of the aorta and pulmonary artery.

Sinus Venosus

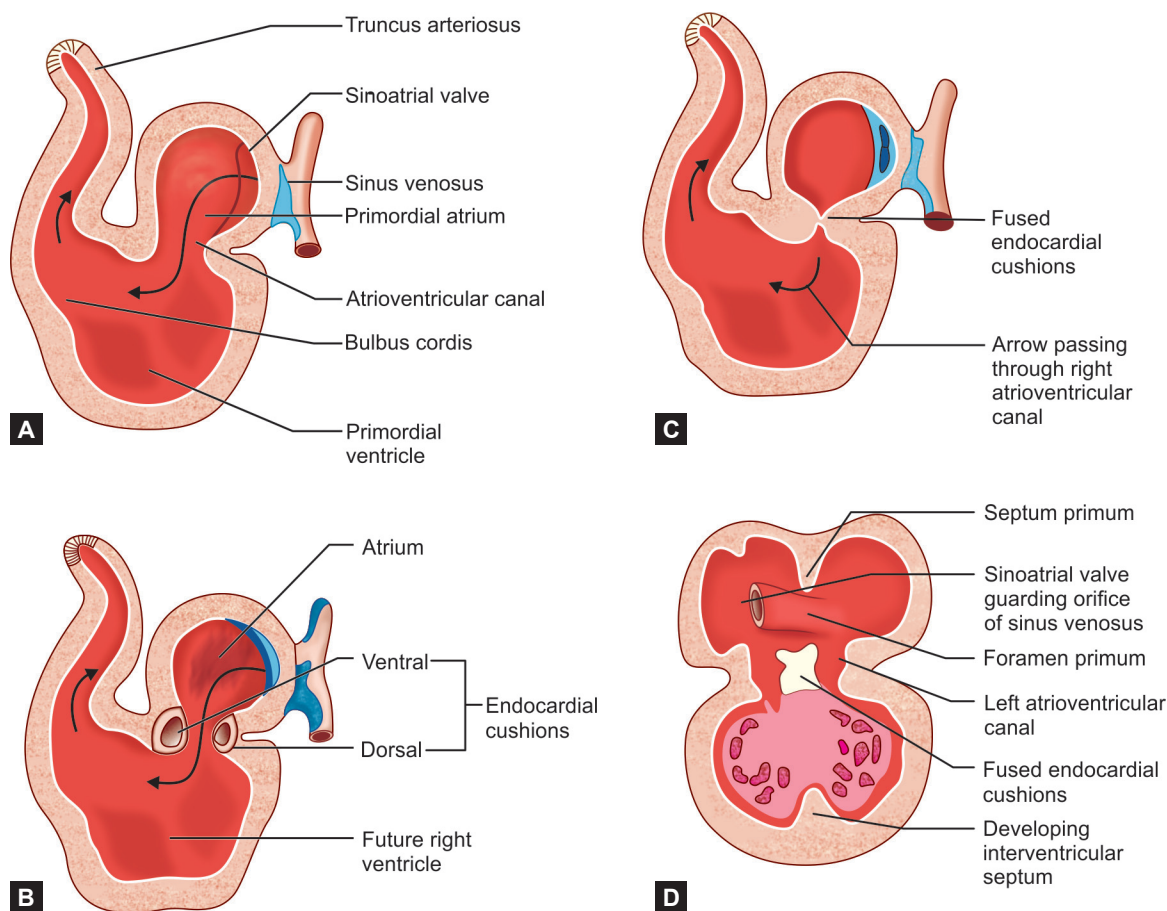
The partial fusion of the heart tubes at the caudal end occurs last and results in the proximal fused caudal sac like sinus venosus which later gets incorporated as atrium and the two distal horns, each of which receives venous return from the umbilical, vitelline and common cardinal veins.

Septum Formation

Two mesenchymal AV endocardial cushions or ridges appear one at the anterior and the other at the posterior border of AVC by the end of fourth week. Right and left AVC passage openings are formed next, with direct communication between atria and corresponding ventricles (**Figs 3A to D**). There is subsequent fusion of both anterior and posterior endocardial cushions with development of two lateral AV cushions by the end of fifth week. Direct communication is established for blood passage between AVC and primitive left and right ventricles.

Interatrial Septation (28–33 Days)

Two interatrial septae are formed one after the other during the fourth week to result in partition of the common atrium. On twenty-eighth day of intrauterine life, *septum primum*, a thin sickle or crescent-shaped endocardial fold starts growing down craniodorsally from a crest in the roof of the common atrium lateral to the sinus venosus opening. The crescent leaves a small opening below its free edge between right and left atria (ostium primum) allowing blood flow across. Two days before it fuses with the AV cushions (thirty-third day) and obliterates the *ostium*



Figures 3A to D (A) Early looping of the heart tube with formation of common AV canal; (B) Formation of dorsal and ventral endocardial cushions on walls of AVC; (C) Formation of septum by meeting and union of endocardial cushions on dorsal and ventral walls of AV canal; (D) Division of the common AV canal into right and left AV canals with beginning of development of interatrial and interventricular septa

primum, small perforations occur by apoptosis at the upper part of septum primum and they coalesce to form a second interatrial communication, the ostium secundum (**Figs 4A and B**).

A thick muscular septum, *septum secundum* arises on thirty-third day craniocaudally from the roof of the atrium to the right of the septum primum and to the left of sinus venosus valve. It stops short of fossa ovalis of the AV cushion. Thus, the interatrial septation is contributed to by both septae overlapping each other.

Formation of Interventricular Septum

Around thirtieth day (5 weeks), the *primary ventricular septum* is formed from a muscular fold which extends from the floor of the anterior wall of the ventricle in a median plane, and continues posteriorly toward the roof to meet the inferior endocardial cushion of the AVC. Dilatation of ventricles on each side results in increase in its length. With further active muscular growth this septum contributes to the muscular portion of the interventricular septum. Till the end of seventh week, there exists a free communication between the two ventricles through a crescent-shaped interventricular foramen formed between the free edge of the septum and the fused endocardial cushions.

Ventricular septation is completed with the meeting of primary muscular septum with the outflow septum and the AV endocardial cushions. The progressive growth of posterior endocardial AV cushion and right (near tricuspid opening) and left (near mitral) bulbar ridges closes the interventricular foramen by the end of 7 weeks. The membranous part of the interventricular septum is formed by the fusion of the two ridges and the endocardial cushion

outgrowth connecting both the muscular ventricular septum and the outflow aorticopulmonary septum in such a manner as to establish the normal reciprocal communications of the right ventricular outflow with the pulmonary trunk and the left ventricle with the aortic trunk (**Figs 4A and B**).

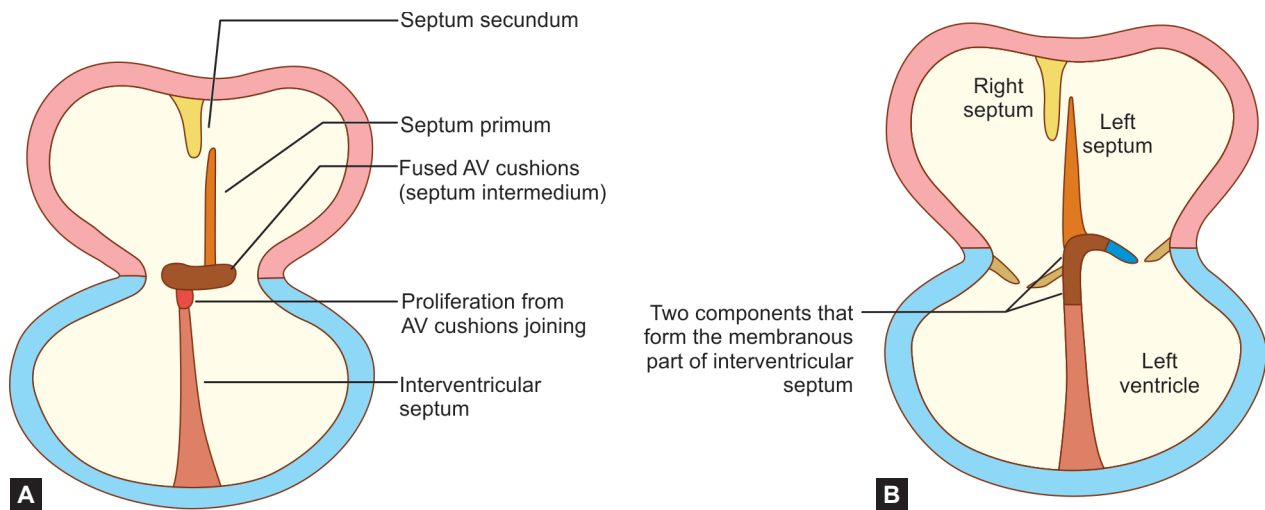
Spiral Septum Formation in the Truncus Arteriosus and Conus Cordis

From the fifth week, pairs of swellings appear on the opposite walls of the truncus, one lying superiorly on the right side and the other inferiorly on the left side. While the right superior truncal ridge grows distally and to the left, the left inferior ridge grows toward the aortic sac but to the right. The characteristics of the growth of these two truncal ridges with final fusion are so programmed so as to form a twisting of these around each other resulting in a spiral aorticopulmonary septum dividing truncus arteriosus into two main arteries: ascending aorta and main pulmonary trunk. Similarly the conal ridges grow and fuse with tissue growth from the inferior endocardial cushion closing the interventricular foramen separating the outflow areas of the ventricle (**Figs 5A to G**).

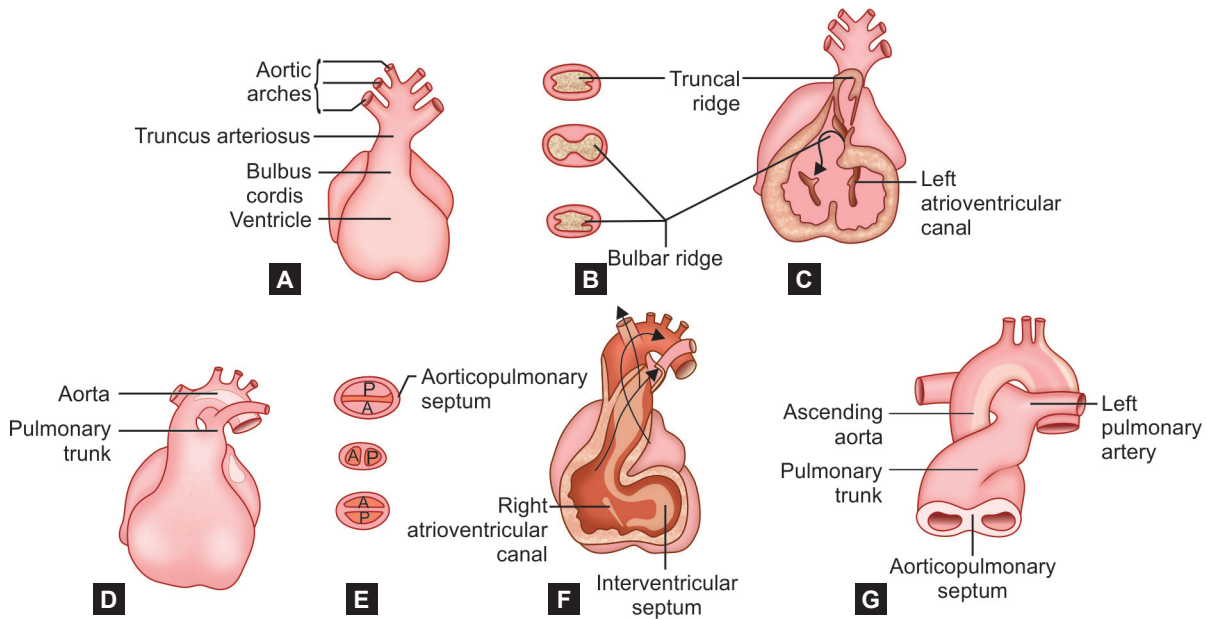
DEVELOPMENT OF MAIN ARTERIAL SYSTEM

Aortic Arch

Aortic sac contributes to the proximal aortic arch; fourth left aortic arch contributes to the main arch and the left dorsal aorta to the distal part of the aortic arch (**Figs 6 and 7**).



Figures 4A and B (A) Development of interatrial septum and interventricular septum; (B) Development of atrioventricular valves



Figures 5A to G From fifth week: (A) Ventral view of heart; (B) Transverse sections of truncus arteriosus and bulbus cordis, illustrating truncal and bulbar ridges; (C) Truncal and bulbar ridges, after removal of ventral wall of heart and truncus arteriosus; (D) Heart after partitioning of truncus arteriosus into aorta and pulmonary trunk; (E) Transverse sections through newly formed aorta and pulmonary trunk showing aorticopulmonary septum; (F) Sixth week: removal of ventral wall to show aorticopulmonary septum; (G) Spiral form of aorticopulmonary septum and aorta and pulmonary trunk twisting around each other as they leave the heart

Fate of First and Second Pairs of Aortic Arches

Major parts of both these arches disappear. A minor component of first aortic arches contributes to maxillary arteries, whereas the second aortic arches contribute to stapedial arteries.

Third Aortic Arch Arteries

Persist as common carotid artery and proximal part of internal carotid artery (both sides). It contributes to the distal part of internal carotid artery by joining with the dorsal aorta.

Fourth Aortic Arch Arteries

On the left side, it contributes to the main part of the aortic arch. On the right side, proximal part of the right subclavian artery is developed from it. The dorsal aorta connecting to the third and fourth arches disappears on both sides.

Fifth Aortic Arch Arteries

No role.

Sixth Aortic Arch Arteries

Proximal parts on both sides form the pulmonary arteries. While the distal part of the right artery disappears, the distal part of the left artery forms the ductus arteriosus connecting left pulmonary artery with arch of aorta.

DEVELOPMENT OF VEINS

Fifth Week of Embryonic Development

Three major pairs of veins are formed, e.g., (1) the vitelline veins (blood from yolk sac to the sinus venosus); (2) the umbilical veins (oxygenated blood from maternal chorionic villi to the fetus),

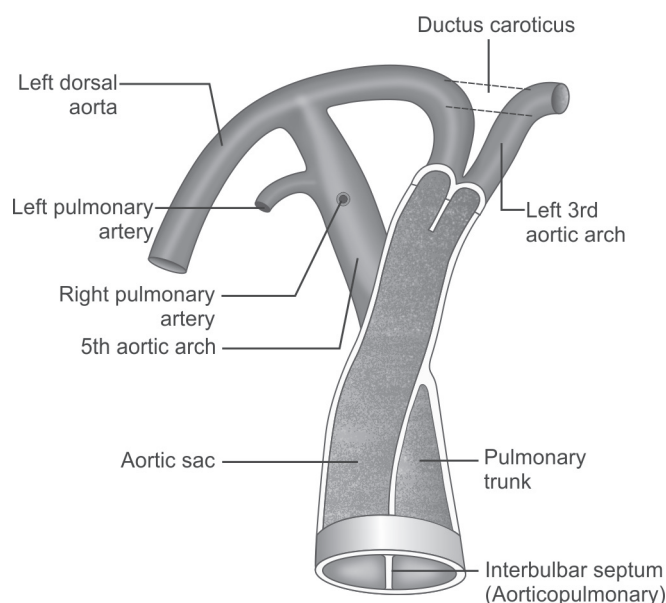


Figure 6 Development of great arteries and their main branches

and the cardinal veins (main venous drainage of the embryo and developing fetus); anterior and posterior cardinal veins drain the respective anterior and posterior regions.

Formation of *ductus venosus* from the left umbilical vein and the right hepatocardiac vein is mandated by the increasing placental circulation as a direct channel to bypass the hepatic sinusoidal plexus. Subsequent to birth of the child, one of the important alterations in the fetal circulation is closure of the ductus venosus to form ligamentum venosus and obliteration of the left umbilical vein to form ligamentum teres of the liver.

Superior Vena Cava

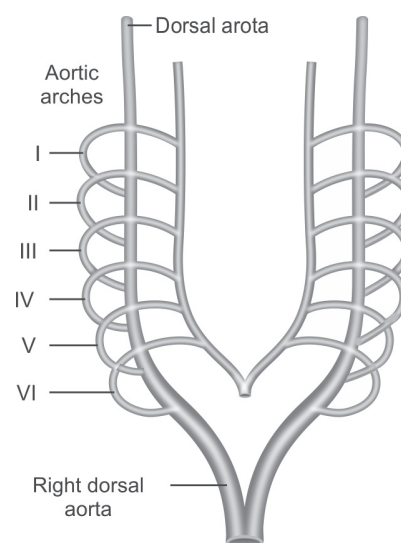
It develops mainly from the right common cardinal vein and proximal part of the right anterior cardinal vein. Inferior vena cava, azygos vein, and hemiazygos vein, are formed from right supracardinal vein, right subcardinal vein, and left supracardinal vein, respectively.

IN A NUTSHELL

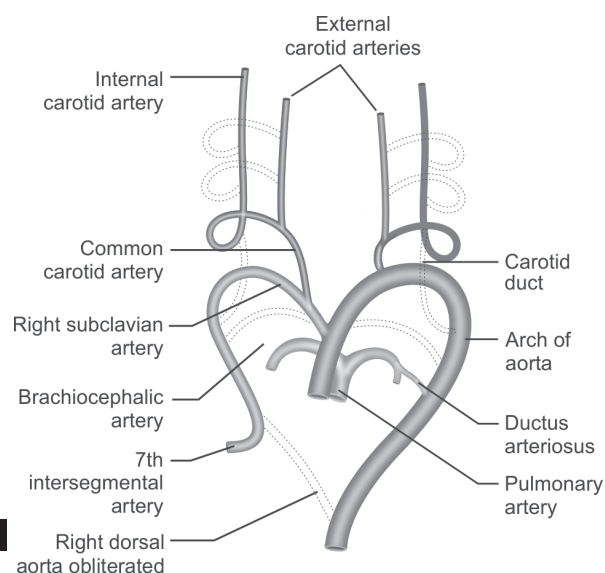
1. Developmental of the heart starts from eighteenth post-connectional day.
2. Formation of heart tube is the first step.
3. Cardiac morphogenesis is almost complete by 8–10 weeks.

MORE ON THIS TOPIC

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A



B

Figures 7A and B (A) Bilateral aortic arches; (B) Its final fate and derivatives

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Chapter 40.3

The Heart and Circulation

Munesh Tomar, Savitri Shrivastava

The systemic venous return to the heart is via the superior vena cava and inferior vena cava to the right atria. In addition to both cavae, right atrium also receives blood from coronary sinus. Eustachian valve guards the opening of inferior vena cava and directs flow from inferior vena cava toward left atria. Right atrium opens into right ventricle via tricuspid valve. Tricuspid valve tensor apparatus attaches both to the ventricular septum (septophillic) and to the right ventricle free wall and is more caudally attached than the mitral valve (normal offsetting of atrioventricular valves). Right atrial appendage is broad, triangular and contains pectinate muscle in it.

Right ventricle is coarsely trabeculated, has three component: inflow, cavity and outflow tract. Right ventricle wall becomes smooth toward the outflow tract. The pulmonary valve connects right ventricle to the main pulmonary artery. Pulmonary valve is supported by the subpulmonary infundibulum, sits higher than aortic valve. Normal pulmonary valve is tricuspid and sits left and anterior to the aortic valve. Main pulmonary artery bifurcates into right and left pulmonary arteries, which connects to respective lungs. Right pulmonary artery has a straighter course, crosses posterior to ascending aorta and below the right bronchus (eparterial right bronchus) to join right lung hilum while left pulmonary artery crosses over the left bronchus (left bronchus-hyparterial) before joining left hilum. Pulmonary blood flow returns to left atrium via four pulmonary veins, two from each lung, and join posterior wall of left atrium. Left atrial appendage is crescent shaped. Left atrium is connected to left ventricle via mitral valve, which is bileaflet, does not have chordal septal attachment (septophobic). The left ventricle is smoothly trabeculated. Aortic valve is tricuspid and sits posterior and right of the pulmonary valve. Right coronary artery arises from right aortic sinus and left coronary from left aortic sinus. Both atria are separated by interatrial septum while both ventricles are separated by interventricular septum. Normal pressure range in all cardiac chambers during infancy and childhood is given in **Table 1**. **Figure 1** depicts the mature circulation.

FETAL CIRCULATION

By the end of 6 weeks of intrauterine life, the heart assumes its normal four-chambered shape. After that minor changes occur and consist mainly in the growth of the heart as a whole with increasing age of the fetus. However, significant differences exist between the fetal circulation and postnatal circulation. Fetal circulation is diagrammatically shown in **Figure 2**. Unique aspect of the fetal cardiovascular circulation is its interface with placenta.

Oxygenated blood enters the fetal circulation via placental transfer. Umbilical vein carries oxygenated blood, which enters the fetus at the umbilicus and course through to join the portal vein. The ductus venosus provides a low resistance bypass between the portal vein and the inferior vena cava so most of the umbilical venous blood shunts through the ductus venosus to the inferior vena cava. Eustachian valve directs inferior vena cava blood across the foramen ovale to the left atrium. The inferior vena caval blood comprising the streams of hepatic veins, umbilical veins, and that reaching the inferior vena cava directly from lower extremities and kidneys. Deoxygenated blood from upper extremity returns via superior vena cava to right atrium and is preferentially directed to the right ventricle. The right ventricle pumps this blood into pulmonary arteries, and across the patent ductus arteriosus into the descending aorta. Due to this streaming of blood in the fetal heart, coronary and carotid arteries get most oxygenated blood while lower body gets perfused with less oxygenated blood. Oxygen content in different cardiac chambers during fetal life is given in **Table 2**.

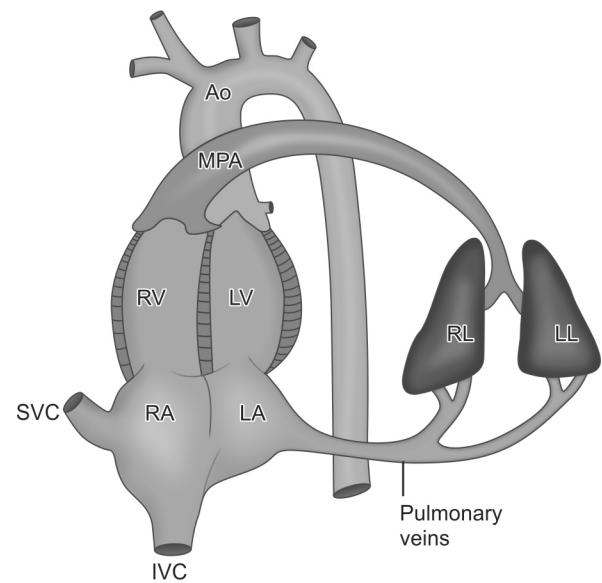


Figure 1 Circulation in children

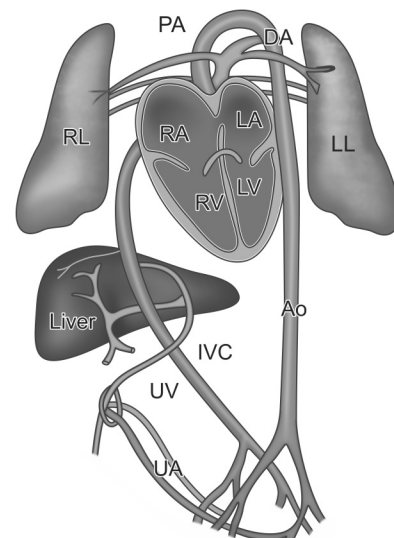


Figure 2 Fetal circulation

Table 1 Pressure range in cardiac chambers in children

Chamber	Pressure (mm Hg)
Right atrium	2–6 (mean)
Right ventricle	15–25/5–8
Pulmonary artery	25/10 Mean 10–16
Left atrium	5–10 (mean)
Left ventricle	90–110/6–12
Aorta	90–110/65–75

Table 2 Distribution, oxygen saturation and partial pressures of oxygen in fetus

Site	PO ₂	Saturation
Umbilical vein	30–35	80–90
Suprahepatic inferior vena cava (umbilical vein + inferior extremity)	26–28	60–70
Superior vena cava	12–14	35–40
Right ventricle and pulmonary artery	18–20	50
Left ventricle and ascending aorta	25–28	65
Descending aorta	20–23	55

Total fetal cardiac output: 450 mL/kg/minute; Right ventricular/left ventricular output: approximately 1.3:1; Most of the available information are from fetal lamb.

During fetal life, as lungs are relatively high resistance unit, only a small amount of blood from right ventricle flows through the pulmonary arteries and veins. In postnatal life two ventricles are connected in series and therefore, the outputs of right and left ventricles are approximately identical. In the fetus very little of the right ventricular output reaches the left ventricle through the lungs, the rest goes through the ductus arteriosus into the descending aorta. The two ventricles are, therefore, acting together in parallel. The left ventricle supplying the head and upper extremities while the right ventricle supplies the trunk, viscera and the lower extremities.

CIRCULATORY ADJUSTMENTS AT BIRTH

Circulatory adjustments occur immediately following birth and continue to occur for a variable period of time following birth. This change is brought about because of a shift from placental dependence for gas exchange in the fetus to pulmonary gas exchange in the neonate.

- Loss of placental circulation with clamping of the umbilical cord, after birth, results in a sudden increase in systemic vascular resistance due to loss of the low resistance placental circulation. This tends to increase the aortic blood pressure and the left ventricular systolic pressure. The left ventricular diastolic pressure also tends to rise and increases the left atrial pressure.
- The loss of placental circulation results in a sudden reduction of flow through the ductus venosus, which closes off. The exact mechanism by which the ductus venosus closes is not known. Flow through the ductus venosus disappears by the seventh day of postnatal life.
- The loss of placental flow results in a decrease in the volume of blood returning to the right atrium. The right atrial pressure decreases. The left atrial pressure becomes higher than the right atrial pressure and the septum primum, which acts as a valve of the fossa ovalis, approximates with the septum secundum to close off the foramen ovale. Functional closure of the foramen ovale occurs very quickly. Over a period of months to years the septum primum and septum secundum become firmly adherent resulting in anatomical closure of the foramen ovale. The foramen ovale functionally closes by third month of life, though probe patent foramen ovale is found in 15–25% of children and adults.
- Sudden expansion of lungs with the first few breaths causes a fall in pulmonary vascular resistance and an increased flow into the pulmonary trunk and arteries. The pulmonary artery pressure falls due to lowering of pulmonary vascular resistance.

The pressure relations between the aorta and pulmonary trunk are reversed so that the flow through the ductus is reversed. Instead of blood flowing from the pulmonary artery to aorta, the direction of flow through the ductus is from the aorta to pulmonary trunk. During fetal life, patency of ductus arteriosus is maintained by the combined relaxant effect of low oxygen tension and endogenously produced prostaglandins. In full-term neonate, oxygen is the most important factor controlling ductus closure. When PO₂ of the blood passing through the ductus reaches about 50 mm Hg, the ductal wall constricts. This effect of oxygen may be direct or mediated by its effects on prostaglandin synthesis. The ductus of preterm baby is less responsive to oxygen. Some functional patency and flow can be demonstrated through the ductus arteriosus for a few days after birth. In full-term neonates the ductus arteriosus closes within 10–21 days. This results in the establishment of the postnatal circulation, which is in series.

APPEARANCE OF MURMUR IN NEONATES WITH HEART DEFECTS

Immediately after birth, the pulmonary pressure and resistance is equal or only slightly lower than the systemic pressure and resistance. Therefore, even if there is a communication between the two sides like atrial or ventricular septal defect or patent ductus arteriosus, there is very little flow from left to the right side. The pulmonary vascular resistance falls fairly rapidly to reach normal adult levels by 2–3 weeks in normal babies. In the presence of a ventricular septal defect or patent ductus arteriosus however, the fall in pulmonary vascular resistance and pressure is slower and reaches adult values around 6–10 weeks. Since there is very little flow across the abnormal communications like atrial or ventricular septal defect or patent ductus arteriosus, they do not manifest in the first few days of life. The ventricular septal defect or patent ductus arteriosus murmurs tend to appear by the middle or the end of the first week of life. It gradually increases in intensity as the pressure and resistance in the pulmonary circuit fall. Only by 6–10 weeks or more when the resistance may have reached its lowest value, the maximum shunt would become apparent.

In atrial septal defect, on the other hand, the right ventricular hypertrophy, present at birth, prevents a large shunt. A thick ventricle cannot expand well in diastole to accommodate a large volume of blood. The right ventricular hypertrophy takes 6 months or more to regress. Thus, the shunt of atrial septal defect takes even longer, i.e., 6 months to become apparent, before these patients are usually identified.

On the other hand, obstructive lesions like aortic stenosis or pulmonary stenosis and valvar leaks like mitral or tricuspid regurgitation would be operative from birth. Some defects as left ventricular to right atrial shunt, arteriovenous fistula are functional from birth as the flow through these defects is not dependent on the fall of pulmonary vascular resistance and these are called as *obligatory* shunts. The flows which are dependent on fall of pulmonary vascular resistance are called as *dependent* shunts. As such the murmur of obstructive lesions as well as valvar leaks would be audible immediately after birth. The clinical manifestations of atrial, ventricular or aortopulmonary communication therefore, show rapid changes in the first few weeks or months of life. Even if the evaluation of an infant at the age of 1 week has been felt to be normal, it does not rule out the presence of congenital heart disease. It is also not possible to correctly estimate the severity of the lesion in the first few weeks of life clinically.

IN A NUTSHELL

1. Fetal circulation is a circulation in parallel while neonatal/adult circulation is in series.
2. Circulatory adjustments at birth are brought about because of a shift from placental dependence for gas exchange in the fetus to pulmonary gas exchange in the neonate.
3. Changes from fetal to neonatal circulation include loss of placental circulation with clamping of the umbilical cord, increase in systemic vascular resistance, closure of ductus venosus, foramen ovale, and ductus arteriosus, fall in pulmonary vascular resistance and an increased flow into the pulmonary trunk and arteries.

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Chapter 40.4

Genetic Basis of Heart Diseases

Sumaira Khalil, Seema Kapoor

Congenital and acquired heart diseases in children result in significant morbidity and mortality posing a major public health problem. Congenital heart diseases (CHDs) are one of the most common causes of birth defects in children. CHDs are defects in either the structure or function of the heart present at birth, with a worldwide prevalence of 14–15 per 1,000 livebirths. Of all the children with CHDs at birth, around 40% present with symptoms in the early/late neonatal period or within first few months after birth and get diagnosed and 33–50% need active intervention within the first year of life.

Genetic factors have been increasingly recognized to play an important causative role in CHDs. Acquired heart diseases presenting in children adolescents like rheumatic heart diseases, essential hypertension, thoracic and aortic aneurysms also have a strong genetic basis. Apart from diagnostics, therapeutic innovations like gene therapy for congestive heart failure have also been explored. Genetic insight and testing has witnessed stupendous technological sophistications and advances that make it possible to identify the genes and point mutations that are responsible for these disorders. This chapter discusses important genetic aspects of both congenital and acquired heart diseases and the developments in diagnostic and therapeutics of heart diseases in children.

EPIDEMIOLOGY

The inheritance in 80% of CHDs is multifactorial resulting from interaction of environmental factors with genetic predisposition. Chromosomal causes, Mendelian inherited disorders or nonsingle gene disorders account for about 20–30% of CHDs. This is definitely an underestimate as the studies have focused more on live born children with CHDs with abortions and stillborn being left out. These figures are however from past few decades where newer genetic diagnostic modalities had not evolved to the current sophistication like genome sequencing.

The term *polygenic* inheritance signifying the interaction of polygenic effects and environmental factors has been the usual explanation for the occurrence of CHDs. Recent studies of transmission risk of various forms of CHD do not fit this model well. The other alternative model is single gene defect modulated by random events. In order to understand the synergy between physiology and genetic-epigenetic interactions one needs to understand the development of the heart.

DEVELOPMENT OF THE HEART

In the gastrulation stage, there are two cell lineages that form the *cardiac* area. The first lineage forms the embryonic heart; the second lineage is derived from an additional *cardiac area* called the second cardiac field. *First heart field* is the crescent-shaped pool of cardiogenic progenitor cells which forms future chambers except the outflow tract. The precursor for the left ventricle is exclusively the embryonic heart whereas, the atria and right ventricle is derived from the cell of both the lineage. The efferent pathway is derived exclusively from the *second cardiac field*. The *second heart field* is the second source of myocardial cells lying medial to the cardiac crescent, and gives rise to a major portion of the heart, anteriorly to the outflow tract and right ventricle

and posteriorly to most of the atria. These findings confirm how mutations associated with CHD give rise to specific defects in heart structure by affecting specific cell lineages in the *second heart field* or in the first heart field. The dorsal neural tube gives rise to the cardiac neural crest cells (cNCC) which migrate into the caudal pharyngeal arches, pharyngeal arches 3, 4 and 6 which give rise to the future blood vessels and the outflow tract which later forms the septum. There are multiple signaling pathways that are involved in the migration of cNCC, including reciprocal signaling between cNCC and second heart field that plays an important part in the development of the outflow tract and the aortic arch system. Understandably, mutations in the genes coding for their formation or signaling would result in CHD.

GENETIC CAUSES OF CONGENITAL HEART DISEASE

With improvement in molecular genetic techniques many genes have been found to be associated with development of the heart. Mutations in a variety of single genes, gross defects in chromosomal number and subtle alterations in genomic regions are associated with a number of selected congenital heart defects and genetic syndromes. The first identified genetic causes of CHD were those with changes in chromosome number like in Trisomy 21 and Turner syndrome. Subsequently, microdeletion syndromes like 22q11.2 deletion or Williams syndrome were also recognized. With newer diagnostic tests like fluorescent in situ hybridization (FISH), multiplex-ligation dependent probe amplification and microarray technologies, larger number of deletions and duplications syndrome are being identified, e.g., 1p36 and 8p23 deletion syndromes (**Tables 1A and B**). The most common form of CHD is the ventricular septal defect which occurs in 30–40% children with CHD. The risks of recurrence in siblings and of transmission of future generations depend upon the exact mode of inheritance. Of the 5–8% of CHD which is due to chromosomal causes the recurrence risk is that of the disorder itself. In about 3% of CHD due to classical Mendelian inheritance, there is a corresponding high recurrence risk in first degree relatives. However, most CHDs have lower risks of recurrence or transmission than that predicted by Mendelian single-gene inheritance.

SPECIFIC ROLE IN DEVELOPMENT OF CONGENITAL HEART DISEASE

The concept of development of CHD arises from a defect in the genetic framework destined for the formation of heart or in the transcription factor or signaling pathway coordinating these timed events. Mutation in any of the components of the numerous regulatory genes or genes involved in the signaling pathways of cardiac morphogenetic regulatory network can cause congenital heart defects. **Table 2** depicts the genes and signal pathways regulating cardiac morphogenesis. The transcription factors are responsible for specific events in the development of the heart. T-box transcription factor gene, TBX 5 was the first single gene mutation identified giving rise to an inherited CHD, the causative gene for Holt Oram syndrome. Mutations in the NKX2-5 have been identified in families with atrial septal defect (ASD) and atrioventricular blocks, ventricular septal defect (VSD), tetralogy of Fallot and Ebstein's anomaly. The cause is haploinsufficiency (absence of one functional allele) of a developmentally important transcription factor, and this could explain the dominant pattern of disease inheritance. There have been studies showing mutations in transcription factor GATA 4 as a possible cause of inherited septation defects. Defective interaction between GATA 4 and NKX2-5 and between GATA 4 and TBX 5 might be the underlying

Table 1A Chromosomal syndromes with associated congenital heart diseases

Chromosomal syndrome	Frequency of CHD		
	All (%)	Cardiac defect	Distinctive or common features
Trisomy 13	50–80	Conotruncal CHD DORV, TOF VSD, ASD, PDA AVSD Polyvalvular dysplasia	Polydactyly Cleft lip and palate CNS anomalies (holoprosencephaly) Renal, GU anomalies Scalp cutis aplasia Microphthalmia
Trisomy 18	95	Polyvalvular dysplasia Conotruncal VSD TOF, DORV AVSD	Overlapping fingers CNS anomalies (posterior fossas) Small facial features Rocker bottom foot Renal, GU anomalies
Down syndrome (Trisomy 21)	40	AVSD defect Complete AVSD Primum AVSD VSD, all types Secundum ASD PDA TOF	GI anomalies Endocrine anomalies Fifth finger clinodactyly Leukemoid reaction Microbrachycephaly
Turner syndrome (45, X)	25	LVOTO CHDs: BAV+AS(v) Coarctation MV anomalies, MVP PAPVC, LSVC Aortic dilatation, dissection Hypertension Prolonged QTc	Horseshoe kidney Short fourth metacarpal Neck webbing Lymphedema Infertility Short stature Nevi, keloids Hypothyroidism

Abbreviations: CHD, congenital heart disease; DORV, double outlet right ventricle; VSD, ventricular septal defect; AVSD, atrioventricular septal defect; TOF, tetralogy of Fallot; BAV, bicuspid aortic valve; LSVC, left superior vena cava; PDA, patent ductus arteriosus; PAPVC, partial anomalous pulmonary venous connection; AS, aortic stenosis; MV, mitral valve; MVP, mitral valve prolapse.

Table 1B Chromosomal deletion and duplication syndromes with associated congenital heart diseases

Chromosome deletion or duplication	Genes	Incidence (%)	Reported CHDs	Other clinical features
Deletion 1p36		35	Assorted CHD TOF/PA PDA Ebstein DCM, noncompaction	Obesity Cleft lip/palate Epilepsy Hearing loss Brachydactyly
Deletion 3p25		33	Primum ASD, AVSD Assorted CHDs	Ptois, abnormal ears Hearing loss Postaxial polydactyly Congenital hypothyroidism
Deletion 4p16	WHSC1 WHSC2	30–50	Secundum ASD PS (v) VSD	Abnormal ears Cleft lip/palate GU anomalies Seizures Hearing loss
Duplication 3q		75	Assorted CHDs	Craniosynostosis Short neck GU anomalies Cleft palate Fifth finger clinodactyly
Deletion 4qter		40	RVOTO PS	Abnormal pinnae Cleft palate Pierre Robin sequence Fifth fingernail tapered, pointed, duplicated
Deletion 5p15		20	Assorted CHD VSD PDA TOF	Cat like cry Cleft lip/palate Abnormal ears Preauricular tags

Contd...

Contd...

Chromosome deletion or duplication	Genes	Incidence (%)	Reported CHDs	Other clinical features
Williams syndrome Deletion 7p13	<i>ELN</i>	75	SVAS+AS(V) PS PPS Coarctation Coronary artery stenosis	Abnormal calcium Hypodontia Characteristic behavior and personality
Deletion 8p23	<i>GATA 4</i>	65–80	PS Secundum ASD AVSD VSD Left ventricular noncompaction	GU anomalies Abnormal ears Minor hand anomalies Diaphragmatic hernia
Duplication 8q (recombinant 8)		45	Conotruncal CHDs TOF, DORV Truncus	Short fifth finger Hypertelorism Hirsutism
Deletion 9p		35	Assorted CHDs	Trigonocephaly Extra flexion creases Hypertelorism Ear anomalies Genital anomalies
Deletion 10p		50	VSD ± ASD PDA	Minor hand/foot anomalies hearing loss renal anomalies DiGeorge phenotype
Deletion 11q23 Jacobsen syndrome		55	VSD LVOTO: HLHS	Thrombocytopenia Abnormal platelets Undescended testis Renal anomalies
Deletion 17p11.2 Smith Magenis syndrome	<i>RAI1</i>	10	Assorted CHD	Brachycephaly Aggressive, self-injurious behavior sleep disturbances eye, ear anomalies
Deletion 18q		15–30	PS ASD VSD	Wide spaced nipples Cleft palate GU anomalies Aural atresia Brain dysmyelination
Tetrasomy 22p Cat eye syndrome		50	TAPVC PAPVC Assorted CHD	Rectoanal anomaly Coloboma Preauricular tag-pit GU anomalies
Derivative 11; 22		60	ASD, VSD, PDA, LSVC	Preauricular tag/pit Cleft palate Genital anomalies
Deletion 22q11.2 DiGeorge sequence Velocardiofacial syndrome	<i>TBX1</i> <i>CRKL</i> <i>ERK2</i>	75–85	IAA type B Truncus TOF VSD	Cleft palate Hypocalcemia T-cell dysfunction Feeding and speech disorder
Conotruncal anomaly face			Aortic arch anomalies	Psychiatric disorders

Abbreviations: DORV, double outlet right ventricle; ASD, atrial septal defect; VSD, ventricular septal defect; AVSD, atrioventricular septal defect; TOF, tetralogy of Fallot; HLHS, hypoplastic left heart syndrome; LVOTO, left ventricular outflow tract obstruction; RVOTO, right ventricular outflow tract obstruction; TAPVC, total anomalous pulmonary venous connection; PS, pulmonary stenosis; PPS, primary pulmonary stenosis; BAV, bicuspid aortic valve; LSVC, left superior vena cava; IAA, interrupted aortic arch; PDA, patent ductus arteriosus; PAPVC, partial anomalous pulmonary venous connection; AS, aortic stenosis; MV, mitral valve; MVP, mitral valve prolapse; DCM, dilated cardiomyopathy.

cause of CHD secondary to *GATA 4* mutation. Currently three interacting transcription factors are identified as regulators of heart formation, and any defective interaction between them leads to inherited CHD (**Table 3**).

GENETICS OF LATE PRESENTING CARDIOVASCULAR DISORDERS

Valvar Heart Disease

The embryological phase of cardiac development is controlled by the multiple genetic programs causing a programmed interplay

of several cell lineages and cellular process. Bicuspid aortic valve, the most common valvar malformation (1–2% of the population) is associated with later development of complications like aortic valve stenosis, regurgitation, infective endocarditis, ascending aortic aneurysm and dissection. NOTCH 2 is a transmembrane receptor functioning as a highly conserved signaling pathway in chorionic villus sampling development. Mutations in *NOTCH 1* and *GATA 5* have been implicated in aortic valvar disease.

The known association of myxomatous degeneration of mitral valve leaflets leading to regurgitation with Marfan syndrome helped in recognizing its genetic etiology—mutations in the

Table 2 Numerous genes and signal pathways regulating the cardiac morphogenesis

Genes/signal pathways	Heart development
<i>NKX2.5</i> , serum response factor (c-fos) serum response element binding transcription factor (SRF), <i>GATA 4</i> <i>TBX5</i> , <i>HAND 2</i>	Core regulatory genes of cardiogenesis and control heart looping, left-right symmetry and chamber formation
<i>FOG2</i> , vascular cell adhesion molecule 1, integrins, erythropoietin and erythropoietin receptor	Epicardial development
Notch homologue receptor (NOTCH), jagged (<i>JAG</i>), WNT, Transforming growth factor beta (<i>TGF-β</i>)2, bone morphogenetic proteins	Cardiac neural crest development in mouse
Retinoic signal acid pathway	Regulation of cardiac looping
Vascular endothelial growth factor, nuclear factor of activated T-cells, cytoplasmic, calcineurin-dependent 1; notch	Complex signal pathways implicated in formation of endocardial cushion and heart valves

Abbreviations: TGF, transforming growth factor; SRF, serum response factor.

Fibrillin 1 gene that altered the transforming growth factor (TGF)- β signaling pathway. This has also attracted pharmacogenetic modification with use of drugs like losartan.

Cardiomyopathies

Dilated cardiomyopathy (DCM) usually refers to the genetic forms of generalized cardiomegaly with heart failure—autosomal dominant in 90% and X-linked in 5–10% of cases—autosomal recessive or mitochondrial inherited forms are very rare. The genes responsible for DCM include genes encoding for sarcomere proteins such as B-myosin heavy chain, cardiac myosin binding protein C, cardiac troponin T, troponin I and myosin light chains. Two other types of cardiomyopathy, e.g., hypertrophic cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy also have a strong genetic background.

Aortic Aneurysmal Disease

Both thoracic and abdominal aortic aneurysms (TAA and AAA) demonstrate a strong genetic component in their etiology. AAA demonstrate associations with variants in/nearby *SORT 1*, low density lipoprotein receptor, *DABZIP*, *LRP1*, *ELN*, *CRP*, *TGF-β* and various matrix metalloproteinase genes suggesting that aberrations of lipid metabolism and proteolytic pathway are the key contributors to the disease. Both syndromic and nonsyndromic TAA are associated with *TGF-β* pathway suggesting a strong genetic basis.

Arrhythmias

The *KCNQ1* gene on chromosome 11 in a region that contains a cluster of 6 genes that are expressed either only in the paternal or maternal allele. Mutations or imprinting of other genes is the cause of long QT syndrome.

Hypertension

Heritability estimates of blood pressure range from 30% to 60%. Monogenic hypertension/hypotension syndromes are rare. The vast majority of elevated blood pressure cases are, however, *essential hypertension* resulting from multiple genetic and

Table 3 Genes associated with congenital heart disease

Diseases	Causative genes	Chromosome location
Congenital heart defects		
Familial congenital heart disease (ASD, atrioventricular block) D-TGA, DORV D-TGA	<i>NKX2.5</i> <i>CFC1</i> <i>PROSIT240</i>	5q34-q35 2q21 12q24
Tetralogy of Fallot	<i>ZFPM2</i> <i>NKX2.5</i> <i>JAG1</i>	8q23 5q34-q35 20p12
Atrioventricular septal defect ASD/VSD Heterotaxy	<i>GATA 4</i> <i>ZIC3</i> <i>CFC1</i> <i>ACVR2B</i> <i>LEFTY A</i>	8p23 Xq26 2q21 3p21.2-p221q42
Supravalvular aortic stenosis syndrome Holt Oram syndrome Alagille syndrome Char syndrome (PDA) Noonan syndrome	<i>TBX 5</i> <i>JAG 1</i> <i>TFAP2B</i> <i>PTPN1 1</i> <i>KRAS</i> <i>SOS 1</i> <i>CHD 7</i>	12q24 20p12 6p12 12q24 2p1.21 2p21 8q12
CHARGE syndrome Ellis-van Creveld syndrome Marfan syndrome Marfan like syndromes Cardiofaciocutaneous syndromes	<i>EVC, EVC 2</i> <i>FBN1</i> <i>TGFBR2</i> <i>KRAS</i> <i>BRAF</i> <i>MEK1</i> <i>MEK2</i>	4p16 15q21.1 3p22 12p12.1 7q34 15q21 7q32
Costello syndrome	<i>HRAS</i>	11p15.5

Abbreviation: ASD, atrial septal defect.

environmental factors. Large genome-wide association studies have revealed many common single nucleotide polymorphisms that associate with blood pressure. Their effects are, however, small and explain only about 2% of the variation of blood pressure even when combined. Further developments are likely to allow insight into deeper associations with factors.

Pulmonary Arterial Hypertension

Many germline gene mutations have now been described, including mutations in the gene coding bone morphogenetic protein receptor type 2 and related genes. Recent advanced gene-sequencing methods have facilitated the discovery of additional genes with mutations among those with and those without familial forms of pulmonary arterial hypertension (PAH) (*CAV1*, *KCNK3*, *EIF2AK4*). The reduced penetrance, variable expressivity, and female predominance of PAH suggest that genetic, genomic, and other factors modify disease expression.

Kawasaki Disease

Kawasaki disease (KD) is a leading cause of acquired cardiac disease of children in the developed countries. The pathogen that triggers this perplexing disease is still unknown after 40 years from the first description. Epidemiologic findings have made us believe that there are considerable genetic components in the etiology and some candidate genetic variations,

which confer susceptibility to KD or risk for coronary artery lesions have been identified. The importance of Ca^{2+} /nuclear factor of activated T-cells pathway in the pathogenesis of KD has been explored.

Rheumatic Fever

Rheumatic heart disease (RHD) is the most serious complication of heart that comprises inflammatory reactions in heart valves. Cytokines play a critical role in triggering inflammatory reactions and they activate the Janus Kinase/Signal Transducers and Activators of Transcription (JAK/STAT) signaling pathway. Polymorphisms of the STAT pathway are likely to confer susceptibility to rheumatic fever. Other susceptibility loci are being explored.

GENETIC TESTING OF HEART DISEASE

The presence of multiple extracardiac malformations, facial dysmorphism and multiple limb anomalies, development abnormalities and growth retardation acts as a marker for recognition of inherited CHDs in children at birth or later. There are several genetic tests available that can help the clinician in establishing the diagnosis. These include cytogenetic tests, FISH and DNA mutation analysis.

In all children with chromosomal abnormalities, around 30% have CHD, while less than 20% of CHD is linked to a chromosomal cause. The standard *metaphase karyotype* (450–550 bands), technique helps in identification of both number and structure. High resolution banding (550–850 bands) is more sensitive in diagnosing duplications, translocations and deletions. *FISH* has helped in the diagnosis of several syndromes like 22q11 deletion syndrome, Alagille and Williams Beuren syndrome. In individuals with major cardiac malformations and mental retardation, having a normal karyotype, *subtelomeric FISH analysis* has a very important role to play in diagnosis. Aortic arch anomalies, ASD, VSD, mitral valve insufficiency and concomitant pulmonary stenosis are the various cardiac malformations reported so far with subtelomeric rearrangements. In recent times the *microarray technique* is a method to obtain very large amounts of gene expression data with a minimum number of experiments.

DNA mutation analysis by Next Generation Sequencing (NGS) has already identified several previously inaccessible disease genes. In suspected 22q known genes like *TBX1* were used in identification. With linkage analysis, a panel of other genes were identified and put together in a chip, i.e., cardiomyopathy panel. Now, the whole human genome is mapped and is available with vast genetic information. This may help in identification of a host of genes to identify subsets of disease where pathway-specific therapies may be available in the near future.

GENE THERAPY IN HEART FAILURE

Gene therapy is aimed at correcting the key pathogenetic mechanisms in the causation of heart failure, wherein targeted drug delivery to myocardium using RNA and DNA is resorted

to as a therapeutic modality to regulate systolic and diastolic performance, reverse myocardial remodeling and restore electric stability. Though there are many inherent challenges in targeted delivery technology, gene transfer into myocardium is likely to become a clinically viable option.

EPIGENETICS

The term *epigenetic* is used to define changes in gene expression resulting from alterations in packing and/or translation of genetic material and not explained by DNA sequence changes. Epigenetic mechanisms can be acquired or inherited and constitute a means by which interactions between genes and environment occur resulting in the occurrence of the disease state. These influences lead to differential expression of similar information depending upon the environmental conditions. It is also likely to explain the influence of various factors such as smoking, drug abuse and hyperpyrexia in the development of the disease. The role of epigenetics, initiated in cancer research is now increasingly being evaluated in the understanding of development and progress of cardiovascular diseases in children and adults.

IN A NUTSHELL

1. A careful search should be made for an underlying genetic cause in CHD in children with associated dysmorphism and multiple congenital anomalies, mental retardation syndrome.
2. Sequencing technology like NGS and whole exome sequencing is likely to unravel multiple genes involved in diseases like cardiomyopathy.
3. Epigenetic and genetic influences play a major role in acquired heart disease.
4. Therapeutic gene manipulation is likely to bring about changes in decompensated stages like heart failure and may be the future for other defects.

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Chapter 40.5

Systemic Disorders with Heart Disease

Anita Khalil

The involvement of the heart and/or blood vessels is known in many systemic disorders including nutritional, infective, metabolic, autoimmune, connective tissue, endocrine and neuromuscular disorders. The involvement of the cardiovascular system may become evident on careful examination and evaluation after the diagnosis of the primary systemic disease gets well-established as in muscular dystrophies or some metabolic disorders. But in a few others, the first clinical presentation of the systemic disorder itself may be an acute cardiac symptom.

NUTRITIONAL DISORDERS

Pediatricians and generalists of earlier days had experienced the dramatic response and improvement of unexplained heart failure after administration of thiamine. Similarly cardiac dysfunction and failure is not uncommon in severely anemic children and adults.

Protein Calorie Malnutrition

Earlier misconception that the heart is rarely affected in severe malnutrition has been shown to be rather ill conceived. Just as wasting of skeletal muscle is noted with inadequate intake of protein and energy, correspondingly a lesser degree of cardiac muscle involvement has also been demonstrated. As myocardial mass decreases, so does the ability to generate cardiac output. However, many of these affected individuals do not have symptoms because of the interplay of various compensatory physiologic mechanisms. Severe cardiac debility results in poor nutrition, which may produce severe myocardial atrophy, which is known as cardiac cachexia, again seen more in yester years with rheumatic mitral valvar heart disease. When such patients are being prepared for cardiac surgery, because of sudden weight loss, they are at risk of sudden death due to arrhythmias. In cardiac cachexia, there is preferential depletion of lean body mass contributing to the weight loss unlike that seen in simple starvation. Experiments on dogs suggest that protein calorie malnutrition seriously interferes with normal LV function with decreased myocardial compliance as a result of *starvation edema* and by reducing myocardial contractility.

Vitamin B₁ (Thiamine) Deficiency

Thiamine (B₁) is not synthesized in humans, and therefore its availability for necessary cellular processes hinges on its continual intake. Severe thiamine deficiency can have severe cardiac and neurologic effects; the former is reflected in a particular type of heart failure called *wet beriberi* which clearly benefits from thiamine supplementation. Clinically these babies manifest with tachycardia, tachypnea, cardiomegaly with dilatation of right heart and pulmonary hypertension.

Anemia and Renal Failure

Severe anemia is often seen to cause congestive heart failure (CHF). Presence of anemia is also associated with more severe systolic and diastolic dysfunction, a higher beta-natriuretic peptide level, increased extracellular volume, with rapid deterioration of renal function. In several controlled and uncontrolled studies, correction of anemia with subcutaneous erythropoietin (EPO) or darbepoetin in conjunction with oral and intravenous iron has been associated with improvement in clinical, cardiac and renal

status. Anemia worsens cardiac function by increasing the heart rate and stroke volume over a period of time thus stressing the heart to perform more efficiently. Reduced renal blood flow and fluid retention adds further to this stress. Longstanding anemia thus results in left ventricular hypertrophy which in turn promotes apoptosis-induced myocardial cell death. These factors operate in a vicious cycle and worsen the heart failure.

The anemia seen in one-third CHF is mainly caused by a combination of decreased renal perfusion and fluid retention. CHF-induced increased cytokine production with anemia-induced renal dysfunction leads to reduced production of EPO, resistance of bone marrow to EPO stimulation. Anemia is further aggravated by iron deficiency due to reduced intestinal absorption of iron and reduced release of iron from iron stores. Renal failure, cardiac failure and anemia therefore all interact to cause or worsen each other—the so-called cardiorenal-anemia syndrome.

INFECTIVE CONDITIONS

Congenital and neonatal viral infections usually display their clinical manifestations in highly recognizable ways. Some of these infections involve cardiovascular system and result in CHDs. Congenital rubella syndrome is associated with patent ductus arteriosus and peripheral pulmonary artery stenosis. Congenital CMV infection may result in cardiomyopathy. Influenza A viral infections may present as fulminant myocarditis resulting in cardiogenic shock and death. Antiretroviral combination therapy for HIV infection is associated with premature manifestation of coronary artery disease. In particular, protease inhibitors have been linked to metabolic changes such as insulin resistance, and abnormalities in lipid metabolism. Endothelial dysfunction is a key event in the initiation and progression of accelerated atherosclerosis which could either be caused by the infection itself or as a side effect of antiretroviral therapy. Cardiac manifestations in hypereosinophilic syndromes may range from heart failure to arterial embolism, which are caused by thickening of the endocardium leading to formation of mural left ventricular thrombus. MRI and echocardiography are able to detect fibrosis, eosinophilic infiltrate and thrombi.

CONNECTIVE TISSUE DISEASES

Marfan Syndrome

Common abnormalities include dilatation of the sinus of Valsalva, of aortic root and ascending aorta with later onset of aortic regurgitation or dissecting aneurysms. Mitral valve and left atrial endocardium often undergo fibromyxoid degeneration resulting in mitral regurgitation and mitral valve prolapse.

Systemic Autoimmune Collagen Vascular Disorders

Cardiovascular involvement may be a major manifestation in rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), primary antiphospholipid syndrome (APS), and systemic sclerosis. Premature atherosclerosis has been reported in RA, SLE, APS, spondyloarthritis and other vasculitis states. Arterial stiffness, coronary arteritis, myocardial, valvar and pericardial diseases are also present in varying proportions during the natural course of these illnesses. Pericarditis is reported in 50% of cases of systemic onset juvenile idiopathic arthritis (JIA). Myocarditis occurs infrequently (1–10%) in JIA, some of which may proceed to cardiomyopathy with its attendant complications like CHF and arrhythmias. Valvar thickening leads on to mitral and occasionally aortic regurgitation. SLE may have pericarditis with pericardial effusion, myocarditis in 10–25% with resulting tachycardia, or Libman-Sacks verrucous endocarditis on mitral valve.

Neonatal Lupus Syndrome

Complete heart block is most commonly diagnosed between 18 weeks and 24 weeks of gestation. It appears that maternal anti-RO (SSA) and La (SSB) antibodies cross the placenta; the latter is a marker for risk of congenital complete heart block, and its absence implies that the child is unlikely to be affected. Mortality approaches 20% and most surviving children may develop cardiomyopathy.

ENDOCRINE DISORDERS

Hyperthyroidism

Thyroid hormones increase oxygen consumption, stimulate protein synthesis and affect carbohydrate and lipid metabolism. It also increases heart rate, cardiac contractility and cardiac output. The systolic and diastolic pressures are increased, mean pressure being unchanged. It may also increase myocardial sensitivity to catecholamines.

Juvenile hyperthyroidism may be associated with tachycardia, high volume pulses, and high systolic and diastolic pressures. The cardiac complications include arrhythmias [supraventricular tachycardia (SVT), nodal rhythm and atrial fibrillation] hypertension and heart failure. In neonates with transient hyperthyroidism, heart failure, arrhythmia (SVT) and mitral valve prolapse have been reported to occur.

Hypothyroidism

Congenital hypothyroidism (cretinism) manifests with significant bradycardia, hypotension and weak arterial pulse with nonpitting facial or peripheral edema. There is low voltage bradycardia with prolonged PR and QT intervals in the ECG and Echo studies may show cardiomegaly, pleural effusion, and asymmetric septal hypertrophy. Pericardial effusion has been reported in older children with acquired hypothyroidism.

Acromegaly

Cardiovascular manifestations include hypertension and dilated cardiomyopathy which contribute to increased mortality associated with the disease.

Pheochromocytoma

Sinus tachycardia and palpitations are the most common symptoms, but serious ventricular arrhythmias, conduction disturbances may also manifest. Reversible dilated or hypertrophic cardiomyopathy is well-established cardiac manifestation with a recent addition of Takotsubo (stress) cardiomyopathy.

Infants of Diabetic Mother

The risk of congenital heart defect is three to four times higher than that of general population, with ventricular septal defect, transposition of the great arteries, truncus arteriosus, tricuspid atresia and coarctation of aorta among the more common defects. Hypertrophic cardiomyopathy with or without obstruction is seen in 10–20% of these infants. The heart is heavier because of increased myocardial fiber size and because of hyperinsulinemia. Infants of diabetic mothers are prone to develop persistent pulmonary artery hypertension.

METABOLIC DISORDERS

Inborn Errors of Metabolism

Myocardial function is very much dependent on energy producing mechanisms like mitochondrial oxidative phosphorylation and ATP producing Krebs citric acid cycle. Hence, it is not surprising to

see either dilated or hypertrophic cardiomyopathies in many of the metabolic disorders involved in these energy producing metabolic processes.

Cardiomyopathy has been reported to be the key or the only presenting feature of fatty acid oxidation defects, e.g., deficiencies of very long chain acyl dehydrogenase, mitochondrial trifunctional protein, and carnitine palmitoyltransferase; glycogen storage disease (GSD) type II (acid alpha glucosidase deficiency) and type IX (deficiency of phosphorylase kinase b), and disorders of oxidative phosphorylation (mitochondrial myopathies). Cardiomyopathy as a secondary feature is observed in GSD types III, IV, mucopolysaccharidosis (MPS), and organic acidemias including propionic, methylmalonic, 3-methylglutaric, d-2-hydroxyglutaric and biotinidase deficiencies.

Fatty Acid Oxygen Disorders

The accumulation of intermediary metabolites of fatty acids, such as long chain acylcarnitines may be responsible for arrhythmias. Inborn errors of fatty acid oxidation should be considered in unexplained sudden death and in those with conduction defects or ventricular tachycardia.

Mucopolysaccharidoses

Excessive amounts of glycosaminoglycans accumulate in myocardium and coronary arteries. The cardiac manifestations are involvement of mitral and aortic valves in more than 50% and cardiomyopathy in 25% of MPS syndromes. Myocardial abnormalities such as septal hypertrophy, dilated cardiomyopathy and endocardial thickening are present in 25% of cases. Occasionally, systemic hypertension is also present. Coronary arterial wall thickening has also been reported in certain forms.

Homocysteinemia

Elevated plasma level of homocysteine is a strong independent risk factor for heart failure in addition to atherosclerotic disease. It causes adverse cardiovascular remodeling, characterized by interstitial and perivascular fibrosis resulting in increased myocardial thickness.

NEUROMUSCULAR DISEASES

Many familial neuromuscular and cardiovascular diseases have shared pathophysiological mechanisms caused by inherited mutations in the cardiac and skeletal muscle cell cytoskeleton, as demonstrated by advanced molecular genetic work-up. Cardiomyopathy is the most common of the cardiac involvement in neuromuscular diseases. Conduction disturbances (Emery-Dreifuss, Kearns-Sayre myotonic dystrophy) and rhythm disturbances are also life-threatening problems in these diseases.

Friedreich Ataxia

Cardiac symptoms include exertional dyspnea and chest pain appearing commonly in those with severe neurologic changes. There is ventricular hypertrophy but the endocardium and the valves are not involved. There is diffuse interstitial fibrosis and fatty degeneration of the myocardium, with compensatory hypertrophy of the remaining cells. A fair degree of atheromatous involvement is present and CHF is the terminal event in 70% of patients.

Muscular Dystrophy

Dilated cardiomyopathy is seen in both Duchenne and Becker muscular dystrophies and manifests clinically during adolescence. Exertional dyspnea and tachypnea are common symptoms and presence of CHF is an ominous terminal event.

Myotonic Dystrophy

Cardiac abnormalities are frequent with involvement of AV conduction and arrhythmias. Fatty infiltration in the myocardium and fibro fatty degeneration in the sinus node and atrioventricular conduction system may be responsible for the manifestations.

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IN A NUTSHELL

1. The involvement of the cardiovascular system is known in many systemic disorders including nutritional, infective, metabolic, autoimmune, connective tissue, endocrine and neuromuscular disorders.
2. The involvement of the heart and vessels may become evident on careful examination and evaluation after the diagnosis of the primary systemic disease OR it may be the first clinical presentation of the systemic disorder.

Chapter 40.6

Cardiovascular Examination

M Zulfikar Ahamed

ARTERIAL PULSE

Arterial pulse wave is a peripheral window to look at heart and starting point for cardiovascular examination. It is related to left ventricular stroke volume, ejection velocity of blood from left ventricle (LV), and capacity and compliance of arterial system. Pulse can be central, e.g., carotid or peripheral, e.g., femoral or radial. A central pulse has an early systolic component (*percussion wave*), later peak in systole (*tidal wave*), an early diastolic component (abrupt negative wave), and a late diastolic component (dicrotic wave). Radial, femoral and other pulsations are peripheral in nature. The pulse changes its character as it becomes peripheral. It assumes greater amplitude, and greater velocity.

Carotid Pulse

It is the major central pulse and is the largest palpable proximal vessel closest to aortic valve; hence the contour resembles that of central aorta. The carotid pulse is best for evaluation of volume and character.

Radial Pulse

Traditionally, pulse rate, rhythm, volume, character and condition of vessel wall are looked for, followed by radiofemoral delay and other peripheral pulses. It is especially useful for assessing pulsus alternans and paradoxus. Pulse rate varies with age. The average pulse rate is 140/min (newborn), 120/min (infants), 100/min (children), and 80/min (adolescents). The arbitrary cut-off points for tachycardia and bradycardia are listed in **Table 1**.

Rhythm

It can be regular or irregular. Minor irregularities in relation to respiratory cycles are common in children especially when heart rate is slow: sinus arrhythmia. Abnormal irregularity in children is often due to ectopic beats, atrial fibrillation or flutter and arteriovenous (AV) blocks.

Volume

It is assessed by feeling both carotids and radials. High volume pulse is present in anemia, thyrotoxicosis, systemic hypertension, aortic regurgitation (AR), mitral regurgitation (MR), patent ductus arteriosus (PDA) and systemic AV fistula. Collapsing pulse is classically found in AR, PDA, systemic AV fistula (SAVF), truncus arteriosus, ruptured sinus of Valsalva (RSOV) and central shunt. In hyperkinetic pulse as in MR pulse pressure is normal, whereas in collapsing pulse, pulse pressure is widened. This pulse is also called Corrigan's pulse or water hammer pulse. Hypokinetic pulse is due to low cardiac output as in severe congestive heart failure (CHF), dilated cardiomyopathy (DCM), myocarditis, aortic stenosis (AS) and multiple sclerosis (MS). In AS, pulse is slow rising, has lower amplitude and the

dicrotic notch occurs later—pulsus parvus tardus. This is best appreciated in carotid artery.

Twice Beating Pulses

When two palpable pulses per cardiac cycle are felt, it is called twice beating pulse. Both pulses can be in systole (bisferiens/bifid) or one in systole and other in diastole (dicrotic). Bisferiens pulse is seen in AR, AR + AS, hypertrophic obstructive cardiomyopathy (HOCM), and occasionally in high output states. Dicrotic pulse is suggestive of impaired LV function, cardiac tamponade, or hypovolemic shock.

Pulsus Alternans

It is best appreciated in radial artery. Alternate strong and weak pulses are felt regularly. It is classically found in significantly impaired LV function and it is also detected by BP difference of more than or equal to 20 mm Hg and could be due to recruitment of more myocardial fibers after a weak contraction, or weak contraction leading to increased end systolic volumes and end diastolic volumes (EDV), and EDV operating through Frank Starling law to improve subsequent contraction.

Pulsus Paradoxus

It is defined as a marked and exaggerated fall in systolic BP (SBP) in inspiration by more than 10 mm Hg. It can be appreciated by a peripheral artery palpation also. Causes are cardiac tamponade, constrictive pericarditis ($\geq 30\%$), severe CHF (RHF), shock, asthma, and emphysema. Occasionally in the presence of tamponade, pulsus paradoxus may be absent in large atrial septal defect (ASD), in associated AR, usually acute; and in hypovolemia. Reversed pulsus paradoxus, i.e., a fall in BP in expiration can be found in HOCM.

Anisophymia

Unequal pulse between right and left radials is called anisophymia. It can occur in coarctation which is proximal to left subclavian artery, Takayasu arteritis, supraaortic AS, post-BT shunt—(classical), aortic arch syndrome, aortic dissection, and subclavian steal syndrome.

Radiofemoral Delay

Weak femorals with bounding radials are found classically in coarctation of aorta usually of thoracic descending aorta. Takayasu arteritis can cause abdominal coarctation and cause weak femorals. A difference in volume between radial and femoral may be more important than radiofemoral delay in an infant with resting heart rate of 120–140/min. In an infant it may be difficult to palpate the femoral, and dorsalis pedis examination is a useful way to exclude a significant coarctation. Coarctation with well-palpable femorals is suggestive of coexisting AR [due to bicuspid aortic valve (BAV)], coexisting PDA, or extensive collaterals to lower limb.

BLOOD PRESSURE

Blood pressure recording consists of recording SBP and diastolic BP (DBP). SBP is influenced by cardiac factors (stroke volume of LV, velocity of ejection), peripheral vascular factors (elasticity, distensibility), and volume in arteries in end diastole. DBP is influenced by peripheral vascular resistance, cardiac cycle length, and compliance of vascular tree.

Blood Pressure Recording

Blood pressure is lowest during sleep, between 2 AM and 5 AM. It has a steep rise from 6 AM to 8 AM and highest BP recordings are in the afternoon (2–4 PM). There is a difference

Table 1 Age-related cut-offs for pulse rate

Age	Tachycardia	Bradycardia
Newborn	> 150/min	< 90/min
Infant and young child	> 120/min	< 80/min
Older child	> 100/min	< 60/min

of 10–20 mm Hg in SBP between upper and lower limbs. Hill sign (difference > 20 mm Hg) is suggestive of AR. False negative Hill sign is found in AR in associated AS, or severe CHF. On standing SBP falls by less than or equal to 10 mm in adults and 5 mm in children. DBP remains the same or becomes mildly elevated on standing. Postural hypotension is defined as a fall of SBP by more than 15 mm in adult and 10 mm in children. Because LV jet preferentially is directed to innominate artery and subsequently to right subclavian artery, right upper limb BP is slightly higher than left upper limb BP. More than 10 mm Hg difference is called anisopphygmia and occurs in all conditions causing anisopphygmia. *Pulse pressure* is between 30 mm Hg and 50 mm Hg. Wide pulse pressure (> 50 mm Hg) is found in fever, anemia, thyrotoxicosis, pregnancy, SAVF, PDA, AR, Truncus and chronic coronary heart disease (CCHD) with collaterals. Narrow pulse pressure (< 30 mm Hg) can occur in CHF, AS, and dilated cardiomyopathy.

Normal Blood Pressure

Normal BP in children is less than 90th centile for age, sex and height centiles for SBP, DBP or both. Between 90th and 95th centile BP is considered *high normal* and above 95th centile BP is abnormal-hypertensive. Value above 99th centile is severe hypertension. A rule of thumb for normal BP in a child is as follows:

$$\text{SBP} : 90 + (\text{Age} \times 2) \text{ mm Hg}$$

$$\text{DBP} : 55 \pm (\text{Age} \times 2) \text{ mm Hg}$$

For SBP, boys will have BP readings 1–2 mm more than girls up to 8 years, will have same BP up to 12 years and again will have slightly higher BP (1–2 mm) up to 18 years. Boys will have DBP slightly higher: 1 mm up to 12 years compared to girls. So the difference according to sex is negligible in childhood. The cut-offs for hypertension at different ages are given in **Table 2**.

JUGULAR VENOUS PULSE

Systemic veins are a low pressure, high compliance system where pressure is between 4 cm of H₂O and 11 cm of H₂O (3–7 mm Hg). Jugular venous pressure (JVP) offers a window to right heart—both right atrium and right ventricle. Normal JVP is assessed by visualizing either external jugular vein or internal jugular vein (IJV). IJV is preferred as it has direct continuity with SVC and hence RA, it has no valves, and it is closer to RA. Right IJV is preferred as it is in direct line to SVC. Normal JVP in children is less than 3 cm from sternal angle. To assess incipient RV failure, sustained pressure is applied by palm of hand over periumbilical area or right upper abdomen for 10–20 sec when patient lies down with quiet breathing with an inclination of 45°. Elevation of JVP of more than 3 cm, or sustained elevation as long as pressure is applied, is considered abnormal. JVP is elevated in following conditions: right heart failure due to any cause; abnormal RV compliance—pulmonary hypertension

(PAH)—pulmonary stenosis (PS)—right ventricular hypertrophy (RVH), pericardial diseases, and obstruction of tricuspid valve/superior vena cava.

Occasionally severe LVH can cause bulging of IVS into RV causing a raised RV filling pressure which in turn can cause increased RA pressure leading to elevated JVP (*Bernheim effect*). Kussmaul sign refers to increase in JVP during inspiration and is suggestive of constrictive pericarditis, or severe CHF.

Abnormality of Wave

A wave is absent in atrial fibrillation. It is large in RVH due to PS-PAH, tricuspid stenosis, and RA myxoma. A giant wave is seen in AV dissociation—in complete heart block, VT (*irregular*), junctional rhythm; and SVT (*regular*). Normally *a* wave is taller than *v* wave in JVP. It can be equal in large ASD and constrictive pericarditis (with elevation of mean pressure).

PRECORDIUM

Inspection

Chest wall is examined for symmetry, precordial prominence, or deformity. Fifteen percent CHD can have associated skeletal anomalies, many of which are in the thorax. They include pectus excavatum, pectus carinatum, kyphosis, scoliosis, and Harrison's sulcus. Look for scars of previous cardiac surgeries. Following pulsations are seen: apex beat, epigastric pulsation, suprasternal, intercostals pulsations including second and third space pulsations.

Palpation

Palpable apical impulse in a normal child is produced by an anterior movement of LV during early systole. Apex beat is clinically the lowermost and outermost definite cardiac impulse felt over precordium and generally reflects LV activity. Normal apex beat is located in fourth left intercostal space (ICS) in midclavicular line—up to 2 years, and in fifth left ICS in 1 cm medial to midclavicular line—beyond 4 years. It is a gentle nonsustained tap, occupies only one intercostal space with a diameter of less than 2.5 cm, and lasts for less than half of systole.

Displaced apex beat indicates cardiomegaly, usually of LV type. Lateral displacement can also occur in scoliosis, straight back syndrome or any intrathoracic pathology like pleural effusion, pneumothorax, congenital lobar emphysema, without true cardiomegaly. In a *hyperkinetic* apex beat, the impulse is forcible and usually lifts examiner's finger tips above the plane of ribs. The duration remains the same: less than 50% systole. This is seen in LV volume overloading conditions [PDA, ventricular septal defect (VSD), SAVF, MR, AR, anemia, thyrotoxicosis and beriberi]. *Heaving* (sustained) apical impulse lifts the fingers markedly and duration of outward impulse is more than 50% systole—it is sustained. The duration of sustained apical impulse is a function of LV ejection time. It is due to pressure overload (AS, CoA, hypertension) but can also occur in other situations (MR, AR, DCM). *Tapping apex* is somewhat similar to normal apical impulse but is more pronounced. It is felt in MS and ASD. Third heart sound (S₃) can be palpated in severe MR and DCM. Palpable S₄ is found in AS, acute MR, hypertrophic cardiomyopathy (HCM), and long-standing hypertension.

Right ventricular activity can be assessed by presence of parasternal heave and epigastric impulse. Parasternal heave or lift can be graded empirically based on amplitude of the lift. The lift can be sustained as in PS or PAH or less well-sustained as in ASD, PR. Left parasternal lift or heave can also be due to severe MR when the systolic rise in LA causes an expansile impulse which can be transmitted to anterior chest wall. It is more diffuse and late systolic in timing.

Table 2 Definite hypertension cut-offs

Age (Years)	Boys		Girls	
	SBP	DBP	SBP	DBP
1–3	> 110	> 55	≥ 107	> 65
4–6	> 115	> 75	> 112	> 75
7–9	> 115	> 80	> 115	≥ 80
10–12	> 125	> 80	< 125	≥ 80
12–15	> 130	> 85	> 130	≥ 80

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure.

Precordial pulsations can be palpated in suprasternal notch (AS, AR, CoA, aortic aneurysm), in second left space (PAH due to any cause), third left space (Ebstein, EMF), and intercostal spaces (hyperkinetic cardiac states). Thrill can be palpated at the apex; left or right sternal border, suprasternal notch, carotids, or in infraclavicular area.

Percussion

It is not very useful in children and may be difficult to perform in infants. Traditionally both right heart border and left heart border are percussed out and occasionally second left space. Right heart border is displaced in conditions of significant RA enlargement, and pericardial effusion. Left heart border is displaced in cardiomegaly, and pericardial effusion.

HEART SOUNDS

First Heart Sound (S_1)

It is a medium high-pitched sound which phonocardiographically has two components. The second component corresponds to mitral valve closure (M_1) and third component to tricuspid valve closure (T_1). Clinically M_1 and T_1 make up S_1 . Normally M_1 is the dominant component and S_1 is best appreciated at apex (mitral area). M_1 - T_1 distance is less than 20 ms and human ear cannot separate them out and hence S_1 is heard normally as a single sound. S_1 is maximally heard at apex and S_2 at pulmonary area. If S_1 heard at apex is louder or equal to intensity of S_2 at PA, it is loud. It is often subjective in evaluation.

Soft S_1 is found in prolonged PR interval, bradycardia (occasionally), chronic AR, chronic MR, acute AR, flail mitral valve, DCM, viral myocarditis, rheumatic carditis, proximal left bundle branch block (LBBB), extracardiac-obesity, emphysema, pericardial effusion and calcific MS. *Loud S_1* is found in MS, TS, LA myxoma, mitral valve prolapse (MVP), tachycardia, short PR interval [Wolff-Parkinson-White syndrome (WPW)] and ASD. *Split S_1* is classically found in Ebstein anomaly, large ASD (occasionally), and right bundle branch block (RBBB). *Reversed split S_1* (T_1 M_1) is quite rare, found in LA myxoma.

Second Heart Sound (S_2)

It has two components: aortic (A_2) and pulmonic (P_2). Normally S_2 is best heard at left upper sternal border, is split in inspiration, and single in expiration. P_2 is softer than A_2 and P_2 is not heard at apex. In inspiration A_2 - P_2 distance is more than 20–30 ms and is appreciated as two components while in expiration the A_2 - P_2 distance is less than 20 ms and is appreciated as a single sound. S_2 is a high pitched sound, best appreciated by diaphragm. The physiological inspiratory widening of S_2 split is due to increased pulmonary artery hang out interval, increased RV ejection time, and decreased Q-A2, i.e., early A2.

Loud S_2 A_2 is loud in systemic hypertension, aortic root dilatation, L-transposition of the great arteries (TGA) (anteriorly placed aorta) and TOF (sometimes). Loud P_2 is present in PAH and ASD without PAH.

Soft S_2 A_2 is soft in severe valvar/supravalvar AS, calcific aortic valve, and AR. P_2 is soft in PS, TOF, and TGA. Wide split S_2 (A_2 - P_2 > 60s in expiration) can be due to early A_2 in VSD, MR and late P_2 in PAH, PS, pulmonary embolism, RBBB, LV ectopic and LV paced beat. Wide-split can also occur due to increased hangout interval in ASD, Ebstein, total anomalous pulmonary venous return (TAPVC) and PS.

Wide and fixed split is characteristic of ASD and severe RV failure. *Reversed split* (P_2 - A_2): *Delayed A_2* -proximal LBBB, right ventricle (RV) pacing, RV ectopic, AS, hypertension, and coronary

artery disease (CAD). Reverse split is also seen in PDA and poststenotic dilatation of AS, due to decreased impedance in aorta. Early P_2 is a feature of right-sided WPW.

Single S_2 can be because of No A_2 (hypoplastic left heart syndrome, aortic atresia), No P_2 (pulmonary atresia, truncus arteriosus, absent pulmonary valve), P_2 masked/very soft—(TOF, TGA, severe PS), or A_2 - P_2 occur together (severe PAH, Eisenmenger VSD, primary PAH).

Third Heart Sound (S_3)

It is a low pitched sound occurring during the rapid filling phase of diastole. The A_2 - S_3 interval is between 120 ms and 200 ms and hence it is not a very early diastolic sound. It is normally heard in infancy, childhood and adolescence and is abnormal beyond 40 years. It is also called a filling sound, ventricular diastolic gallop or protodiastolic gallop.

Pathological S_3 is found in all causes of LV dysfunction, large left to right shunts: VSD, PDA, atrioventricular septal defect, chronic AR, MR, restrictive cardiomyopathy, DCM, myocarditis, rheumatic carditis, constrictive pericarditis (*pericardial knock*), PAH, systemic hypertension, anemia, thyrotoxicosis, and systemic AV fistula.

Pericardial knock is an early, loud, higher pitched S_3 in constrictive pericarditis. A_2 -PK distance is usually 80–110 ms. It has a clicking quality and is due to marked elevation of filling pressures associated with increased velocity of rapid filling phase.

Fourth Heart Sound (S_4)

It is a low frequency sound. It is also called atrial sound, atrial gallop and presystolic gallop. However, it is ventricular in origin. It precedes S_1 . In children S_4 is abnormal. It is absent in AF. It can be left-sided: increases on expiration, right sided: increases on inspiration. Causes in childhood are: HCM, aortic stenosis, anomalous left coronary artery from the pulmonary artery (ALCAPA) with CAD, acute AR, DCM, acute MR, AV block, and systemic hypertension. S_4 is usually looked for in left lateral position with the bell and is sometimes palpable. RV S_4 is found in severe PAH.

Clicks

Clicks are sharper, higher pitched sounds heard in systole. Clicks can be ejection clicks or nonejection clicks. Ejection clicks originate from either, semilunar valves aorta, or pulmonary artery. Causes are aortic valve stenosis (BAV), pulmonary valve stenosis; systemic hypertension, aortic dilatation, AR, aortic aneurysm, TOF (due to aortic dilatation), PAH and idiopathic dilatation of pulmonary artery.

Valvar ejection clicks are due to sudden doming and snapping of semilunar valve during ejection and nonvalvar clicks are due to tensing of dilated great vessels.

Aortic valve ejection click due to BAV or AS at valvar level. It indicates valvar nature of AS and mobility of valve. Click is constant in expiration and inspiration, i.e., constant ejection click. It is heard in AS, BAV and truncus.

Pulmonary valve ejection click is phasic in nature, i.e., increases on expiration and decreases in intensity in inspiration in contradistinction to the general rule that all right-sided cardiac auscultatory events increase in inspiration. S_1 -EC distance progressively decreases as PS progresses. Ejection click can occur both in PS and PAH. In PS, as it becomes severe, EC occurs earlier, as PAH progresses EC occurs later. In PS click is phasic, while in PAH it is usually constant. **Table 3** summarizes differences between aortic and pulmonic click.

Table 3 Aortic versus pulmonary click

	<i>Aortic click</i>	<i>Pulmonic click</i>
Maximum at	Aortic area, apex	Pulmonary area
Conduction	Carotids, widely	Localized
Relation to respiration	Constant	Phasic
Additional features	Low volume pulse	Normal volume pulse
	Left ventricular apex	Left parasternal heave
	Thrill at aortic area	'a' wave in JVP
	Paradoxical split	Thrill at pulmonary area
		S ₂ loud with wide split

Nonejection click is a high pitched sound which could be slightly lower pitched than ejection click. It is classically found in MVP and tricuspid valve prolapse. It is usually midsystolic in timing and can be late systolic in timing also. Mid-systolic nonejection sounds (clicks) also can be found rarely in LA myxoma, adhesive pericarditis, and left pneumothorax.

OPENING SNAP

It is pathognomonic of atrioventricular valve obstruction, classically MS. It is a crisp, high pitched sound heard at apex, and best appreciated between apex and left LL sternal border. It may be widely conducted if severe MS is present. It represents mobility of the valve and is due to sudden arrest of doming mitral valve. A₂-OS interval is 40–160 ms, and it is the earliest diastolic sound. As MS becomes severe A₂-OS interval shortens. It also occurs in TS and atrial myxoma. Functional snap in diastole can be heard in large ASD, VSD, thyrotoxicosis, tricuspid atresia with large ASD, severe MR, TR, HOCM, and MVP.

Prosthetic Valve Sounds

Usually from mechanical valves can occur in children who have undergone mitral or aortic valve replacement. Sounds can be opening and closing and is more prominent with ball and cage valves than disc valves. Sharpness of the valve clicks indicates the health of the valves. Bioprosthetic valves do not have an early systolic sound.

Pacemaker Sound

Children with permanent pacemaker implant have a pacemaker sound which is extracardiac in origin due to stimulation of intercostal muscles and is high pitched.

Pericardial Rub

Is a high pitched, leathery, scratchy murmur best heard over left lower sternal border. It has three components: presystolic, systolic, and late diastolic. Usually rub is constituted by presystolic and systolic elements causing a to and fro nature of the rub. Rub need not disappear with pericardial fluid collection.

HEART MURMURS

Murmur is the most frequent reason for referral for a child or infant with suspected heart disease: whether congenital or acquired. Yet many CHD—both benign and malignant—can present with hardly any murmur. In some CHD, a cardiac murmur is either not essential or useful for the diagnosis, example being ASD and

coarctation of aorta. But a murmur still continues to be a major marker for heart disease and also has significant localizing value—in localizing the clinical diagnosis. In infants with cardiac murmur, one-fourth presented before 2 weeks and one-third presented only after 3 months. Detection of a heart murmur should prompt one to initiate a complete evaluation of an infant or child. Murmurs can be systolic (between S₁ and S₂), diastolic (between S₂ and S₁), or continuous. They can be further classified as organic (**Box 1**) or innocent.

BOX 1 Murmur likely organic when:

- There is a diastolic murmur
- There is a continuous murmur
- Murmur is of Gr 3/6 or more
- Murmur is either pansystolic or early systolic
- When S₂ is abnormal
- When associated CVS findings are present.

Systolic Murmurs

Early Systolic Murmur

It starts with S₁ (S₁ coincident) and extends variably into systole and stops short of S₂. It is usually decrescendo. Causes are acute MR, TR with a normal right ventricular systolic pressure, very small, restrictive VSD, and very large, unrestrictive VSD with significant PAH.

Mid Systolic Murmur

The murmur starts a little after S₁, and usually ends before S₂. Majority of such mid systolic murmurs are ejection systolic murmurs, i.e., it is due to phasic flow through LV and RV outflow tract. Causes include AS, PS, PAH, ASD, aortic root dilation and Still's murmur.

Late Systolic Murmur

The murmur begins well after S₁, begins in mid or late systole and travels variably into systole. It is classically found in MVP and also found in TVP and has no ejection quality.

Pansystolic Murmur (Holosystolic)

It begins with S₁ (S₁ coincident) and occupies all of the systole up to S₂ (or S₂ on its side of origin) and is constant in shape and amplitude usually. Examples include VSD, aortopulmonary window, PDA in infancy, MR and TR.

Diastolic Murmurs

Early Diastolic Murmur

It is S₂ coincident murmur. It begins with S₂, is decrescendo in nature and travels variably into diastole. Examples are AR and PR.

Mid Diastolic Murmurs

It starts in mid-diastole and occupies variable phase of diastole. They are usually low pitched murmurs. It occurs in MS, TS, LA myxoma, MR, TR, VSD, PDA, ASD (flow related), and AR (Austin Flint murmur).

Late Diastolic Murmur

It is also called presystolic murmur which ends with S₁. It commonly occurs in sinus rhythm only in stenosis of mitral or tricuspid valves.

Continuous Murmur

Continuous murmur begins in systole, continues without interruption into diastole—into all or part of diastole. It usually peaks around S_2 . Continuous murmurs are generally generated when blood flows from one (high pressure) vascular bed to another (low pressure) vascular bed without interruption (**Tables 4 and 5**). It is to be differentiated from to and fro murmur which is interrupted at some point of time (**Box 2**).

Conduction of the murmur can be often useful in diagnosis. Murmurs of MR conducts to axilla, back and occasionally to base; PS conducts along supraclavicular area to acromion, base of neck; AS conducts to carotids, and VSD conducts along sternal border, widely heard in infants.

All heart lesions may not be associated with a murmur. There are several heart defects where the murmur is either absent or insignificant (**Table 6**).

MORE ON THIS TOPIC

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BOX 2 To and fro murmurs

- Ventricular septal defect with aortic regurgitation
- Absent pulmonary valve syndrome
- Aortic stenosis with aortic regurgitation
- Pulmonary stenosis with pulmonic regurgitation.

Table 4 Continuous murmurs

Innocent murmur	Organic murmur	
	Acyanotic conditions	Cyanotic conditions
1. Venous hum	1. PDA	1. Pulmonary AV fistula
2. Mammary	2. RSOV	2. PDA in CCHD
Soufflé	3. AP window (in 10%)	3. Aortopulmonary collaterals
	4. Coronary AV fistula	4. Truncus arteriosus
	5. Systemic AV fistula	5. Unobstructed supracardiac TAPVC
	6. ALCAPA	6. BT shunt in CCHD
	7. Aorticoatrial fistula/tunnel	7. ASD with mitral atresia
	8. Lutembacher with small ASD	
	9. Coarctation of aorta	
	10. PA branch stenosis	

Abbreviations: PA, pulmonary artery; TAPVC, total anomalous pulmonary venous connection; BT, Blalock-Taussig; CCHD, cyanotic congenital heart disease; PDA, patent ductus arteriosus; RSOV, ruptured sinus of Valsalva; AP, aortopulmonary; AV, arteriovenous; ALCAPA, anomalous origin of left coronary artery from pulmonary artery; ASD, atrial septal defect.

Table 5 Variation in murmur intensity with maneuvers and drug (Hemodynamic auscultation)

Increases in expiration	Left ventricular heart sounds LVS_3 , LVS_4 Murmurs of MR, MS, AS, AR
Increases in inspiration	Right ventricular heart sounds LVS_3 , LVS_4 Murmurs of TR, TS, PS, PR
<i>Variation of auscultatory heart sounds and murmur with postural changes</i>	
Increases on standing	HCM, MVP
Decreases on standing	AS, PS, innocent
<i>Variation with squatting</i>	
Increases	AR, MR, AS, PS, TR
Decreases	MVP, HCM
<i>Variation with handgrip</i>	
Increases	MR, AR, VSD, MS
Decreases	MVP, HCM
<i>Variation with Valsalva strain</i>	
Increases	HCM, MVP
Decreases	AS, PS
<i>Variation in systolic murmur with amyl nitrite inhalation</i>	
Increases	ASD, HCM, AS, TR, PS
Decreases	MR, AR, VSD, PDA, TOF
<i>Variation in diastolic murmur with amyl nitrite inhalation</i>	
Increases	MS, PR (Nonhypertensive)
Decreases	AR, AFM, PR (PAH)

Abbreviations: LVS, left ventricular systolic; MR, mitral regurgitation; MS, mitral stenosis; AR, aortic regurgitation; AFM, Austin Flint murmur; RAH, right atrial hypertrophy; ASD, atrial septal defect; HCM, hypertrophic cardiomyopathy; MVP, mitral valve prolapse; TR, tricuspid regurgitation; TS, tricuspid stenosis; AS, aortic stenosis; PS, pulmonary stenosis; PAH, pulmonary hypertension.

Table 6 Heart defects with absent/insignificant murmur

<i>Infancy</i>	d-TGA, severe TOF, PA with VSD, pulmonary atresia with intact IVS, obstructed TAPVC, severe CoA, aortic atresia, myocarditis, dilated cardiomyopathy, EFE, Pompe disease, ALCAPA, HCM, Ebstein's anomaly
<i>Childhood</i>	Dilated cardiomyopathy, viral myocarditis, coarctation of aorta, severe TOF with high PCV, pulmonary AV fistula, hypertensive heart disease, pericardial effusion, constrictive pericarditis
PA with VSD: pulmonary atresia with VSD	

Abbreviations: EFE, endocardial fibroelastosis; HCM, hypertrophic cardiomyopathy; TOF, tetralogy of Fallot; PA, pulmonary atresia; VSD, ventricular septal defect; IVS, interventricular septum; TAPVC, total anomalous pulmonary venous return; ALCAPA, anomalous origin of left coronary artery from pulmonary artery.

Chapter 40.7

Electrocardiogram

BRJ Kannan

Electrocardiogram (ECG) is a simple and useful tool in the diagnosis and management of heart diseases in children. It also gives important clues regarding presence of dyselectrolytemia. Its most important role is in detection and management of arrhythmias. With its inherent limitations in the diagnosis of structural heart disease, it provides information regarding the pressure and volume overload changes in cardiac chambers, supplementing the clinical and chest X-ray findings.

BASICS OF RECORDING AND INTERPRETATION

While recording ECG in a small child, limb lead electrodes should be placed more proximally to reduce motion artifacts. The usual 12 lead ECG is not enough; additional V3R or V4R leads have to be recorded in children with suspected congenital heart disease. Standard gain (10 mm/mV) is used. If the QRS voltages are very large, then the gain might be halved.

The ECG is recorded at a paper speed of 25 mm per second. The time or duration of a wave is measured in milliseconds or seconds. Each small square represents 40 ms (0.04 seconds). The voltage is measured in small squares or millivolts (mV). Each small square represents 0.1 mV. Intervals should be hand measured, as the computerized systems are often inaccurate, especially in the neonates.

Intervals in children increase with increasing age, reaching the adult normal values by 7–8 years of age. The PR interval is measured from the onset of the P wave to the onset of Q wave or R wave (if no Q wave is present). It is often best measured in lead II. The duration of QRS complex is measured in the lead with an initial Q wave. The QT interval is often best measured in leads II, V5 and V6 and the longest value should be used. Corrected QT (QTc) is calculated using Bazett's formula.

$$\text{Corrected QT} = \text{QT interval} / \sqrt{\text{RR}}$$

Heart Rate Calculation

$$\text{Heart rate} = \frac{1,500}{\text{Number of small squares in a RR interval}}$$

For example, if there are 15 small squares between two consecutive R's, then the heart rate is 100/min (1500/15).

Axis Detection

Select leads aVF and I. Determine if the net QRS voltage is positive or negative in these leads. For example, if the R wave height is 10 mm (above the isoelectric line), and S wave height is 3 mm (below the isoelectric line), then the net QRS voltage is positive (+7). If the R wave is short and S wave is longer, the net QRS voltage would be negative (Fig. 1). The QRS axis can be located using the rules given in Box 1.

At birth, right axis deviation of mean QRS vector is the rule. The axis becomes normal by 1 year of age. Hence, normal or leftward QRS axis is abnormal in the neonatal period and early infancy. Common conditions with leftward axis of QRS vector are *tricuspid atresia* and *AV septal defects*. QRS axis can be normal or

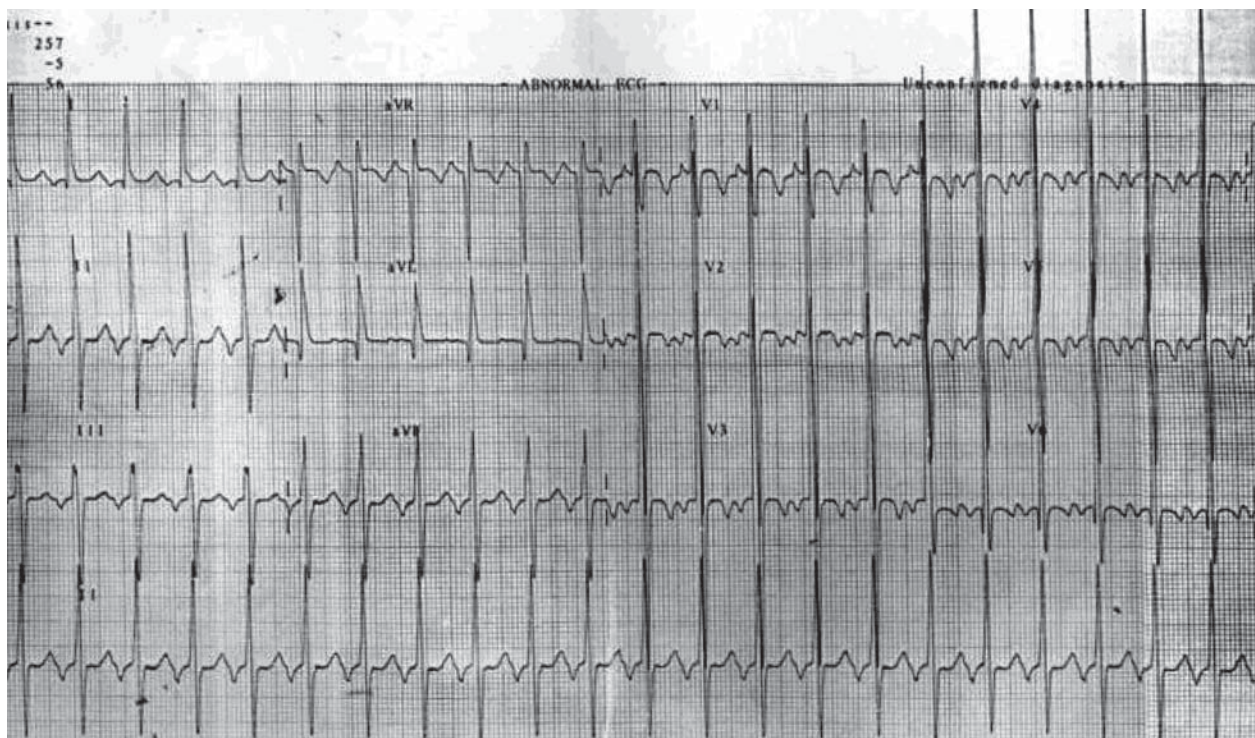


Figure 1 Narrow QRS tachycardia. There is a P before each QRS and this could be wrongly labeled as sinus tachycardia. The Ps are inverted in the inferior leads suggesting that it is nonsinus rhythm. This long RP tachycardia is called permanent junctional reciprocating tachycardia

BOX 1 Detecting the axis

Lead I	Lead aVF	Interpretation	Comment
Positive	Positive	Normal axis	Abnormal in neonates and early infancy
Negative	Positive	Right axis deviation	Normal in neonates and in early infancy
Positive	Negative	Left axis deviation	Abnormal at any age
Negative	Negative	North-west axis	Abnormal at any age

leftward even at birth in very premature babies (< 28 weeks) as RV dominance is not a feature at this age.

NORMAL VARIATIONS AND RELATED ABNORMALITIES

Many tables of ECG standards for various measurements are available. However, the practical utility of these tables is limited. The salient age-related changes that one needs to know are as follows:

- Normal HR in the neonates varies between 120/min and 230/min; it increases further by first or second month of life and gradually decreases over the next 6 months. Resting heart rate is about 120 beats/min at 1 year, 100 beats/min at 5 years and reaches adult values by 15 years.
- Appearance of secondary *r* waves (*r'* or *R'*) in right chest leads is normal in neonates.
- Dominant R in right precordial leads can persist up to 6 months to 8 years; in the majority, the R/S ratio in lead V1 becomes less than 1 by 4 years.
- Q waves are normally seen in leads II, III, aVF, V5 and V6.
 - If Q waves are seen in other leads, it is abnormal.
 - Presence of Q wave in inferior leads (II, III and aVF) is due

to clockwise loop of initial QRS vector. This finding is seen in majority of congenital heart diseases also.

- When Q waves are absent in inferior leads but are seen in leads I and aVL, it is due to counterclockwise loop of the initial QRS vector. This is a feature of tricuspid atresia, atrioventricular (AV) canal defects and inlet ventricular septal defect (VSD).
- Deep Q waves in lateral leads might point toward underlying anomalous origin of left coronary artery from pulmonary artery.
- QT interval is highly variable in the first 3 days of life. If the corrected QT is more than 0.44 seconds (440 ms), it is abnormal.
 - Prolonged QT interval: Common causes: Hypokalemia, hypocalcemia, hypothermia, and cerebral injury.
 - Drug-induced QT prolongation has to be ruled out (e.g., macrolide antibiotics, trimethoprim, cisapride, etc.).
 - Consider congenital long QT syndromes, if clinically relevant and other known causes are ruled out (European Society of Cardiology).
- T wave in lead V1 can be upright at birth and it inverts by 7 days and typically remains inverted until 7 years of age. Upright T waves in right precordial leads (V1-V3) between ages 7 days and 7 years usually indicate right ventricular hypertrophy even if the voltage criterion is not fulfilled.
- Atrial and ventricular extra systoles are common and are typically abolished with exercise. Also, sinus arrhythmia is very common and there could be irregularly irregular rhythm (**Fig. 2**). The heart rate slows in expiration and speeds up in inspiration. Some children would present with significant sinus bradycardia. Both these conditions are due to excessive vagal tone. Exercise consistently increases the heart rate and the rhythm becomes regular in these children.
- Sinus pauses as long as 800–1,000 ms can be seen especially during feeding, sleep, defecation or other times of increased vagal tone. At times, periods of junctional rhythm, i.e., narrow QRS complexes without preceding P waves may also be seen.

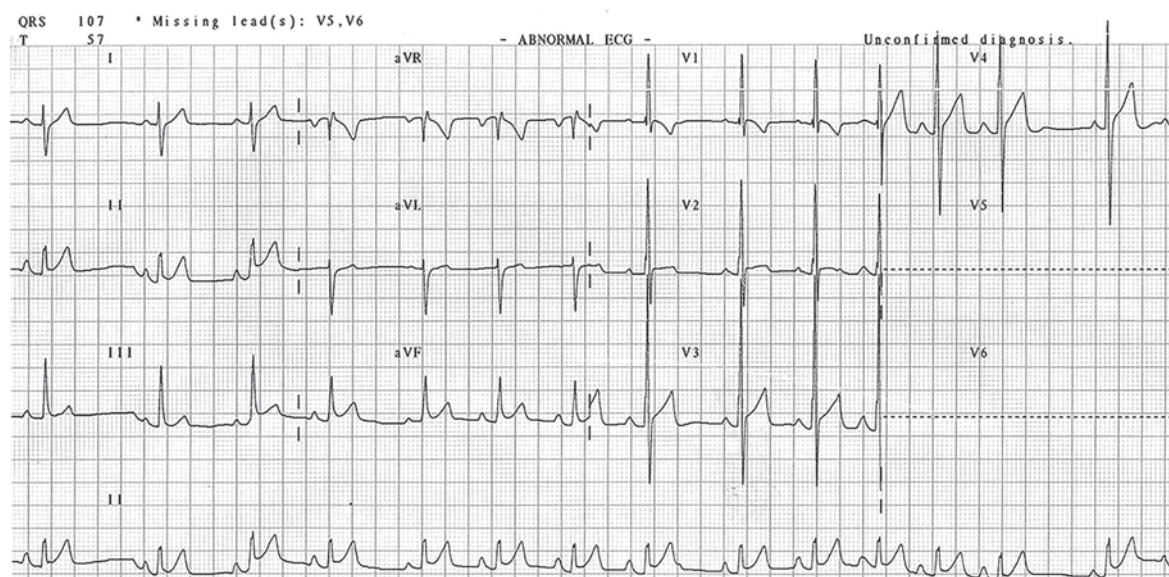


Figure 2 There is significant irregularity of the rhythm. However, all QRS complexes are preceded by P waves with constant PR interval. This is due to sinus arrhythmia. Note the ST-segment elevation with concavity facing upward due to early repolarization. Both the findings are normal in children

- **Wandering pacemaker:** Change in P wave axis and morphology in different beats due to the shift of pacemaker from the sinus node to other sites. It is a nonpathological finding.
- **Early repolarization:** Some children especially in the adolescent age group would show ST segment elevation of 1–4 mm with the concavity facing upward (**Fig. 2**). They can also have terminal T wave inversion.

P Wave

P wave amplitude varies very little with age. Unlike QRS axis, P wave axis is normal (positive in both lead I and aVF) from birth due to sinus nodal origin of the atrial impulse. If the P axis is different, it indicates ectopic atrial rhythm, i.e., the atrial impulse arises from some other site. Low atrial origin of the rhythm is common in congenital heart disease where the P waves are typically negative in inferior leads (II, III and aVF). In children with situs inversus, right axis deviation of the P wave is seen (**Fig. 3**).

Right Atrial Enlargement

P wave amplitude is increased to more than 0.25 mV (2.5 mm) with a relatively normal P wave duration (*tall and peaked P waves*). The changes are best visualized in lead II. Tricuspid atresia, pulmonary atresia with intact ventricular septum and severe pulmonary stenosis are commonly associated with right atrial enlargement.

Left Atrial Enlargement

The changes are best visualized in lead V1 where the terminal negative deflection is increased (> 0.1 mV) and prolonged (> 40 ms). Prolonged P wave duration with increased notching can be seen in lead II due to left atrial enlargement but it is less specific. Mitral atresia and post-tricuspid shunts [VSD, patent ductus arteriosus (PDA), aortopulmonary window] show left atrial enlargement.

PR Segment

PR segment reflects the time taken by the depolarization impulse to travel across the atrium and the AV node. AV block results in prolongation of the PR interval.

First degree block Prolonged AV interval.

Second degree block, Mobitz Type I (Wenckebach type) With each successive beat, the PR interval lengthens resulting in a dropped QRS. This could be a normal finding and does not usually indicate an adverse prognosis.

Second degree block, Mobitz Type II The PR interval is normal or mildly prolonged but it is constant in successive beats. There is sudden, intermittent loss of conduction resulting in dropped QRS. This is always pathological, carries high-risk to progress to complete AV block.

Third degree AV block This is also called as complete heart block (CHB) where no atrial impulse is conducted to the ventricles. Atrial rate would be higher than the ventricular rate with complete AV dissociation (**Fig. 4**). If the escape rhythm originates near the His bundle, the resulting QRS would be narrow. If the escape focus is lower down, the resultant QRS complex would be broad. Congenital CHB is often not associated with any underlying congenital heart disease. About 2–5% of mothers with autoimmune antibodies have children with CHB and this condition carries a high mortality risk especially in the first 3 months. CHB can be also seen in children with congenitally corrected transposition of great arteries and AV canal defects. Acquired CHB can be seen in myocarditis, digitoxicity, following cardiac surgery and rarely, after interventional procedures such as catheter closure of the membranous VSD.

Causes of Short PR Interval

Common causes are Wolff-Parkinson-White syndrome (WPW syndrome), ectopic atrial pacemaker from the low right atrium, mannosidosis, Fabry disease and Pompe disease.

Wolff-Parkinson-White Syndrome (Pre-excitation)

It is due to premature conduction of atrial impulses to ventricles through accessory pathways resulting in delta wave and a fusion complex in the ECG (**Fig. 5**). The pre-excitation may be subtle and only detected in the mid precordial leads. The prevalence in children has been estimated to be 0.15–0.3%, higher in those with structural heart disease. Congenital heart diseases with higher prevalence of WPW syndrome are: Ebstein's anomaly of tricuspid

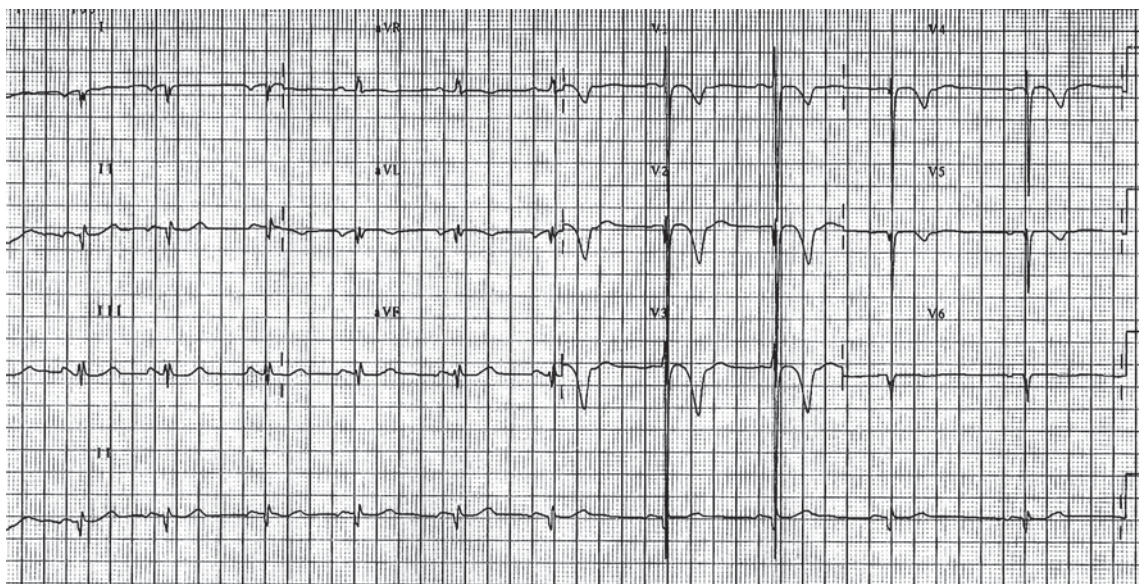


Figure 3 There is right axis deviation of P wave as it is negative in lead I and positive in lead aVF. This is consistent with atrial situs inversus. The chest leads show progressive reduction of the QRS size without the normal progression of R wave, which is suggestive of dextrocardia

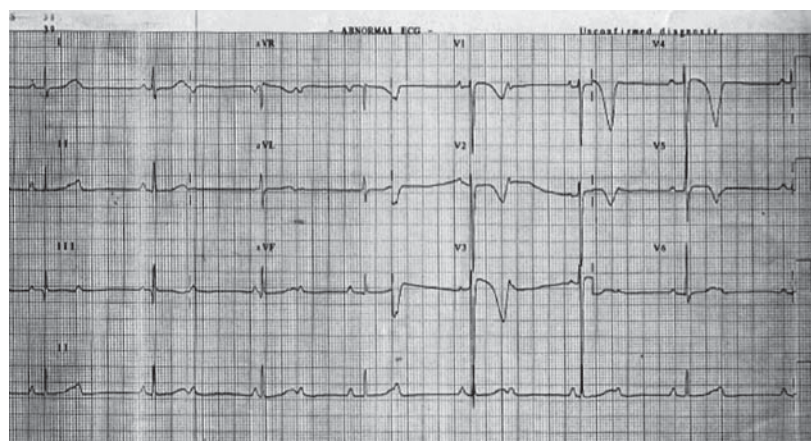


Figure 4 Complete heart block: Atrial rate is 110/min and the ventricular rate is 45/min. PR interval is not constant suggestive of AV dissociation

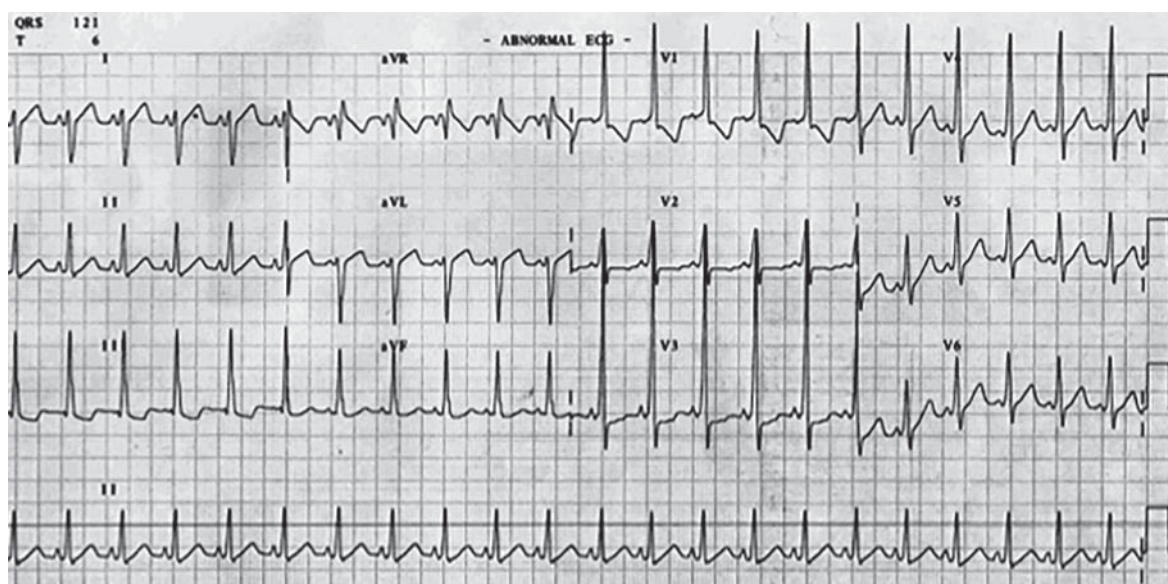


Figure 5 Wolff-Parkinson-White syndrome: Short PR interval is seen. The slurring of initial portion of R wave (delta wave) is seen in all leads, especially V1

valve, congenitally corrected transposition of great arteries, hypertrophic cardiomyopathy and cardiac rhabdomyoma.

Wolff-Parkinson-White syndrome is the most common cause of paroxysmal supraventricular tachycardia (SVT) in children. The incidence of sudden death has been estimated to be as high as 0.5% and cardiac arrest may be the initial presentation. Hence, it is very important to identify this electrical abnormality. Digoxin and verapamil have to be avoided in this condition and beta-blocker therapy is the ideal choice.

QRS Complex

Bundle Branch Blocks

Intraventricular conduction abnormalities due to bundle branch blocks (BBB) are uncommon in normal children. BBB results in wide QRS duration of more than 0.14 sec or more. Right BBB is diagnosed if V1 shows tall wide notched R (rSR' pattern) and the lateral oriented leads (lead I, V5 and V6) show notched wide S wave. In left BBB, the lateral leads show tall notched R wave and V1 shows wide notched QS or rS complex. Right BBB is commonly seen following open-heart surgery.

Right Ventricular Hypertrophy

Many congenital heart diseases are associated with right ventricular hypertrophy. Tall R in V1 ($R/S > 1$), deep S in V6 and upright T wave in right precordial leads indicate the presence of right ventricular hypertrophy. Conditions with pressure overload of right ventricle, e.g., valvar pulmonary stenosis show small q and tall R pattern or only tall R could be seen (**Fig. 6**). Conditions with volume overload of right ventricle, e.g., atrial septal defect shows rSR' pattern.

Left Ventricular Hypertrophy

It produces increased voltages in the left-sided leads and manifest as tall R wave in leads V5, V6 and deep S wave in lead V1 (**Fig. 7**). No definite criteria based on the voltages are available to diagnose ventricular hypertrophy in children. Another important clue for the presence of left ventricular hypertrophy is the presence of T wave abnormalities in leads V5 and V6.

- Tall T waves would indicate underlying volume overloading condition (VSD, PDA).
- ST depression and T inversion in lateral leads could result from pressure overloading of left ventricle (aortic stenosis, coarctation of aorta).

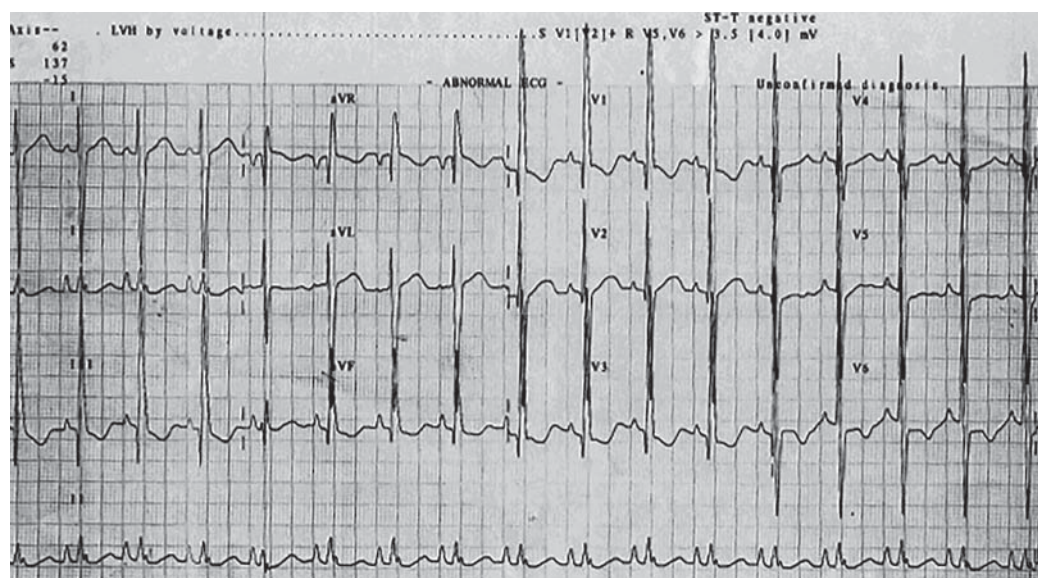


Figure 6 Right ventricular hypertrophy: There is right axis deviation of QRS. Tall R wave, ST depression and T inversion in leads V1-3 is suggestive of right ventricular hypertrophy with pressure overload strain

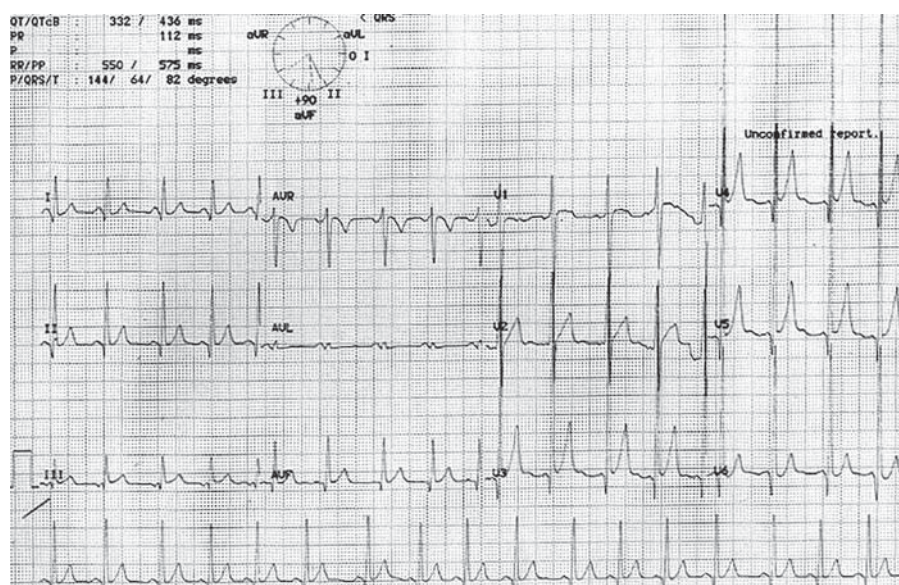


Figure 7 Left ventricular hypertrophy: Tall QRS complexes in the lateral leads with ST depression and T inversion due to pressure overload of LV

- Peculiarly, neonates with coarctation of aorta have ECG features of right ventricular hypertrophy (and not left ventricular hypertrophy) as the right ventricle receives a greater proportion of systemic venous return from the SVC and faces the systemic vascular resistance in the fetal period through the ductus arteriosus.
- In children with post-tricuspid shunts, large amplitude equiphasic QRS complexes could be seen in the mid precordial leads suggestive of biventricular hypertrophy (Katz-Wachtel phenomenon).

Cardiac Position-Related QRS Changes

In levocardia, the major portion of the ventricles is positioned to the left of the midline with the apex pointing to the left. The

chest leads show a progressive change from a dominant S wave in lead V1 to a dominant R wave in leads V5 and V6. In children with dextrocardia where the major portion of the ventricles is to the right of midline, this normal progression is not seen. Instead, there is progressive reduction in the amplitude of QRS from V2 to V6 (**Fig. 3**). In these children, right-sided leads are commonly taken in the positions corresponding to the left-sided leads that would show *normal* progression of QRS complexes. However, further interpretation of the right-sided leads regarding chamber enlargement is not possible.

ST Segment

ST segment elevation is commonly due to early repolarization as mentioned above. The next common cause is pericarditis.

Other causes are: hyperkalemia, intracranial hemorrhage, pneumothorax or pneumopericardium. Structural anomalies that can cause ST segment elevation are anomalous origin of left coronary artery from pulmonary artery and Kawasaki disease-related coronary arteritis. The former more commonly presents with deep Q waves in leads I, aVL, V5 and V6 with associated T wave inversion. Brugada syndrome is a genetic disorder associated with a high incidence of sudden death due to ventricular fibrillation. ECG in this condition shows ST segment elevation with RBBB pattern in the right precordial leads.

ST segment depression is seen secondary to pressure overload strain. In right ventricular strain, ST depression is seen in right precordial leads while it is seen in left precordial leads in left ventricular strain.

T Wave

In children, T wave is inverted in V1-V3 between 7 days and 7 years. At times, T remains inverted in older children and adolescents (*persistent juvenile T*). As mentioned above, upright T wave in V1 would indicate right ventricular hypertrophy even in the absence of high amplitude R wave.

- T wave inversion in lateral leads represents relative or absolute ischemia and is a feature of ventricular pressure overload strain, anomalous left coronary artery from the pulmonary artery (ALCAPA) and Kawasaki disease with coronary involvement.
- Tall T wave is one of the ECG manifestations of hyperkalemia. Other manifestations of hyperkalemia are disappearance of P wave, broadening of QRS wave, ST segment disappearance resulting in sine wave.
- In hypokalemia, there is gradual reduction in the amplitude of T wave with eventual disappearance of T wave while U wave appears.

DISEASE-SPECIFIC ECG CHANGES

Most of the common congenital heart diseases like tetralogy of Fallot, D-transposition of great arteries, total anomalous pulmonary venous connection, truncus arteriosus, pulmonary atresia, hypoplastic left heart syndrome show Q waves in inferior leads (leads II, III and aVF), RVH and right axis deviation of the QRS

vector, the ECG pattern does not help distinguish one condition from the other. However, absence of above mentioned features point toward some other diagnosis.

Tricuspid Atresia

Q wave in leads I and aVL; left axis deviation of QRS, right atrial enlargement, dominant LV forces in the chest leads (**Fig. 8**).

Common AV Canal Defect

Q wave in leads I and aVL, left axis deviation of QRS, both right ventricular and left ventricular forces are seen (biventricular hypertrophy pattern).

Corrected Transposition of Great Arteries

Normally interventricular septum is depolarized from left to right, that results in Q waves in lateral leads (leads V5 and V6). In this condition, as the ventricles are inverted, the septal depolarization is also reversed. Hence, *q* waves are absent in V5 and V6, but can be seen in right precordial leads (V3R, V1).

Ebstein's Anomaly

Giant P waves, RBBB pattern, low voltage complexes (especially in limb leads). Look for the presence of delta wave, as WPW syndrome is commonly associated. The accessory pathway is usually right sided and hence V1 will show deep S wave (**Fig. 9**).

Pompe's disease This condition produces apparent hypertrophy of the ventricles due to accumulation of glycogen. Short PR interval, very tall QRS complexes in multiple leads (**Fig. 10**).

Dilated Cardiomyopathy

In idiopathic dilated cardiomyopathy, ECG may be normal or show broad QRS complexes in sick patients. However, in any case of cardiomyopathy, two common treatable causes that need to be ruled out are ALCAPA and tachycardiomyopathy. ECG signs of ALCAPA are ST depression and Q waves in lateral leads (leads V5, V6, I and aVL) (**Fig. 11**). Persistent high heart rate should make one to suspect the ongoing tachycardia. Even when the suspicion is small, it is useful to administer adenosine and record the effect on the rhythm.

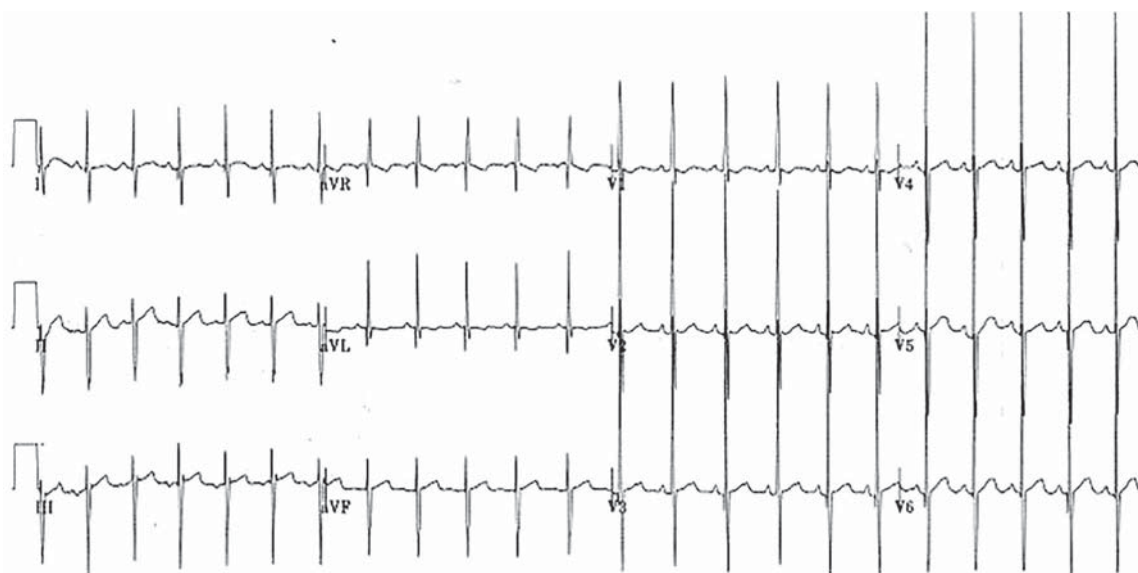


Figure 8 Tricuspid atresia: Left axis deviation of QRS, Q waves in leads I and aVL and absence of RV forces in right-sided leads

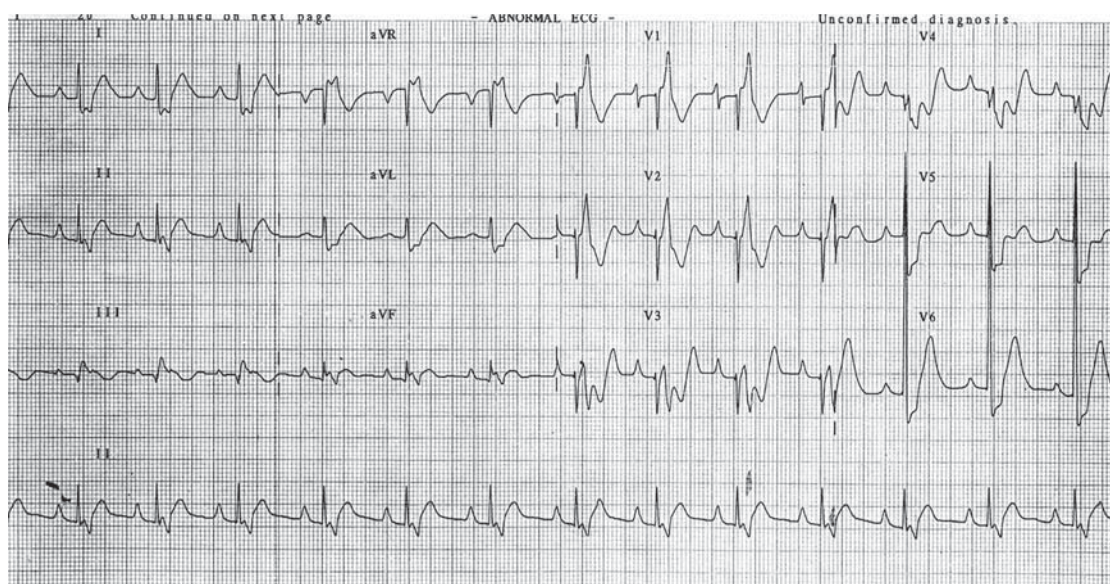


Figure 9 Ebstein's anomaly: Tall P waves due to right atrial enlargement. Broad and bizarre QRS complexes of RBBB morphology typically seen in this condition

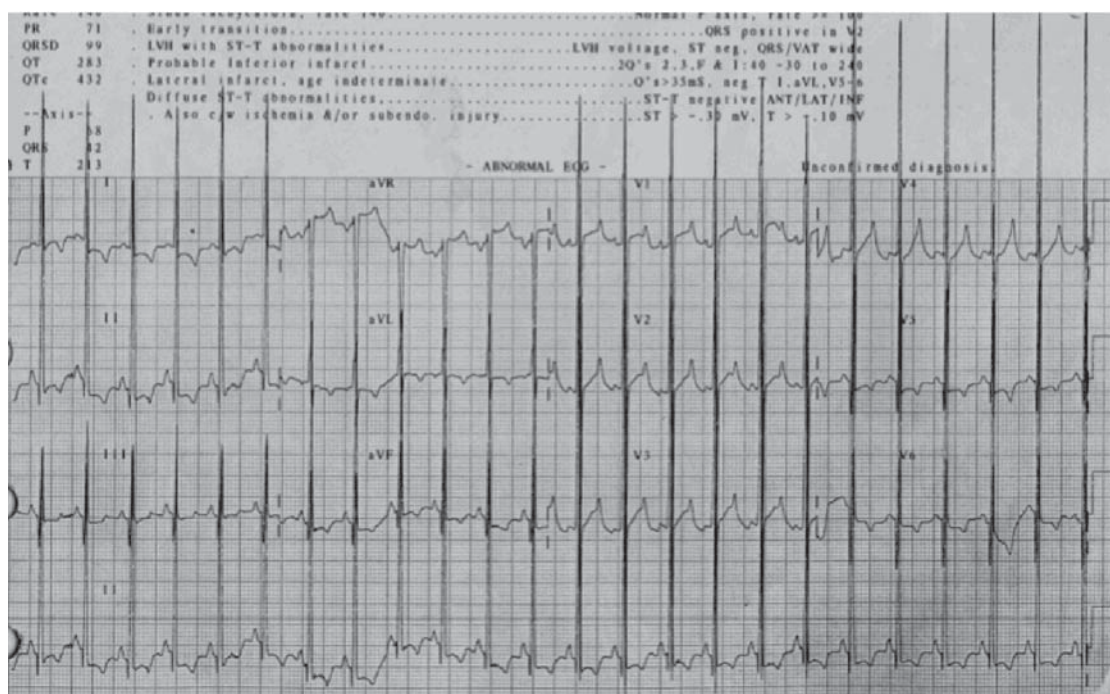


Figure 10 Pompe disease: Very tall QRS complexes in all the leads with relatively short PR interval

Pericarditis

ST elevation is seen in almost all the leads with its concavity upward. In addition, there is PR depression (**Fig. 12**).

ARRHYTHMIAS

In any child presenting with tachycardia, it is important to document the rhythm with a 12-lead ECG unless the child is hemodynamically

compromised. It is particularly useful to record the effects of administration of medications such as adenosine because important clues to the underlying arrhythmia are unraveled. SVT is much more common than ventricular tachycardia (VT). QRS complex is narrow and similar to that of sinus rhythm in SVT. If the QRS complex is different from sinus, VT should be diagnosed even if the QRS is relatively narrow. Any wide QRS tachycardia should be considered as VT until proved otherwise.



Figure 11 Anomalous left coronary artery from the pulmonary artery: Note the deep Q waves in leads I, aVL, V5 and V6. These leads also show ST depression and T wave inversion

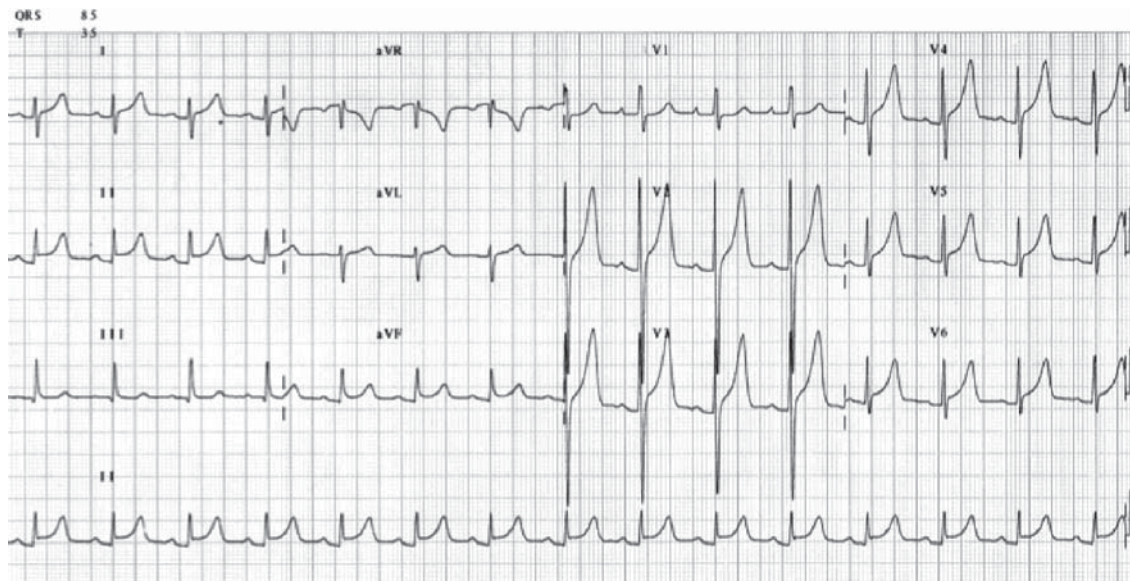


Figure 12 Pericarditis: ST elevation is seen in almost all the leads with its concavity upward. In addition, there is PR depression

MORE ON THIS TOPIC

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Chapter 40.8

Chest Skiagram in Heart Disease

BRJ Kannan

A systematic approach to interpret chest X-ray (CXR) is quintessential in the management of cardiac illnesses in children. This would entail training one's mind to observe routinely for several diagnostic parameters, a short list of which would include assessment of the following: (1) situs, (2) cardiac position, (3) cardiac/chamber enlargement (4) arch sidedness, (5) lung vasculature, (6) lung parenchyma, (7) bony cage, and (8) diaphragm.

RADIOLOGICAL ASSESSMENT OF THE HEART SHADOW

Situs and Cardiac Position

Situs refers to the location of organs. There are three parameters to assess with respect to this:

1. *Abdomen for visceral situs:* In the abdomen, liver is normally on the right side and stomach on the left. This normal position corresponds to *situs solitus*. This is identified in the CXR by the location of the gas shadow in the gastric fundus.
2. *Chest for visceral situs:* In the chest, location of the three lobed and bilobed lungs corresponds to the organs in the abdomen. The right bronchus is broad, short and takes a vertical course while the left bronchus is narrow, long with a more horizontal lie.
3. *Atria for cardiac situs:* Atrial position corresponds to the position of the organs in the chest and abdomen, i.e., if the liver is on the right side, right lung is trilobed and RA would be on the right side.

Normally, major portion of the ventricles and the apex are located in the left side of the chest and this is termed as *levocardia*. If the apex is seen in the right side of the chest, it is called *dextrocardia*. If the heart takes a vertical position in the center of the chest, it is called as *mesocardia*. It is important to know and remember that the position of the ventricles need not always correspond to that of the atria.

In a situs solitus situation where the RA would be on the right side, ventricles need not always be facing the left, i.e., a child can have dextrocardia even if the situs is solitus. Hence a child could have any of the combinations shown in **Box 1**. If we are not able to clearly define the situs, i.e., midline stomach with ill-defined bronchial shadows, it is termed as situs ambiguous.

Cardiac Chamber Enlargement

The right heart border is formed by superior vena cava (SVC) and RA. The left heart border is formed by aortic knuckle, left atrial (LA)

appendage and left ventricle (LV). Main pulmonary artery lies at the slight concavity between the aortic knuckle and the LA appendage. Apex is formed by the LV. However, these are applicable only to those with situs solitus, levocardia with normal atrioventricular and ventriculoarterial connections.

Normally, cardiothoracic ratio (CTR) is less than 55%. The right heart border is just beyond the right border of thoracic spine. At times, an enlarged ascending aorta, as seen in bicuspid aortic valve, could form the right heart border. Significant shift of the right border would mean enlargement of atria, especially RA. LA dilatation might not produce obvious cardiomegaly. A shadow within shadow (outline of LA would be seen within RA) and more horizontal shift of left bronchus are the signs of LA enlargement in CXR. Heart more commonly enlarges in the left side, usually due to LV dilatation. Greater the dilatation, more would be the downward and outward shift of the cardiac apex. Isolated RV enlargement causes minimal cardiomegaly in the anteroposterior CXR. Upturned apex is a sign of RV enlargement.

Aortic Arch Sidedness

Normally the ascending aorta arches over the left bronchus and descends along the left border of thoracic spine. This arrangement is referred to as left-sided aortic arch. Normal hearts and most of those with CHD will have left aortic arch. If the arch is right sided, it is an important clue for the underlying *conotruncal anomalies*. If the pulmonary blood flow (PBF) is normal or increased, it would suggest truncus arteriosus and if the PBF is reduced, it would suggest tetralogy of Fallot (TOF).

Aortic arch sidedness is usually identified by the prominent aortic knuckle. However, it might not be discernible and could be masked by the thymus shadow in infants. A more consistent sign is to look for the tracheal indentation caused by the arch.

Lung Vasculature

A dilated main PA is easily identified by the prominent round shadow below the aortic knuckle. The right pulmonary artery branch courses horizontally to the right. Hence, this is also easily visible in the CXR if enlarged. The left pulmonary artery branch courses anteroposteriorly. Hence, it is not seen in the anterior posterior projection of the CXR. However, its peripheral branches are visible in the lung fields. Correct exposure and penetration is needed for the proper interpretation of PBF.

The number of end on view appearances to assess the degree of PBF is neither sensitive nor specific. An increased radiolucent (blackish appearing) lung fields would suggest reduced PBF; large central and peripheral branches of PA would suggest increased PBF. Repeated readings of CXRs with various degrees of PBF is the surest way of proper interpretation.

Increased PBF is a feature of left-to-right shunts and admixture lesions like single ventricle. Decreased PBF is seen in TOF, its variants and severe Ebstein's anomaly.

Lung Parenchyma

Pneumonitis and pulmonary congestion/edema are common features of those conditions that cause increased PBF. If the opacity is predominantly located near the hilum, it may be secondary to early pulmonary edema. A more florid pulmonary edema would show opacities distributed in all the lung fields. A uniform ground glass haze is indicative of severe pulmonary venous obstruction and is seen in obstructed (usually infradiaphragmatic) total anomalous pulmonary venous drainage (TAPVD). This will mimic the picture of respiratory distress syndrome and one should always consider the possibility of this surgically correctable cardiac lesion in neonates and infants. Hypoplasia or collapse of

BOX 1 Combinations of visceral, atrial and ventricular situs

Gastric shadow	Left atrium	Cardiac apex	Situs	Cardiac position	Figure
Left	Left	Left	Solitus	Levocardia	1A
Left	Left	Right	Solitus	Dextrocardia	1B
Right	Right	Right	Inversus	Dextrocardia	2B
Right	Right	Left	Inversus	Levocardia	2A

a lobe of lung would result in shift of the cardiac shadow toward that side. It is a consistent feature of Scimitar syndrome where right lower lobe hypoplasia results in shift of the cardiac shadow toward the right.

Bony Cage and Diaphragm

Rib notching (Dock's sign) is a very uncommon feature of coarctation of aorta these days because of early recognition and intervention. It is seen only after 10 years of age due to sclerosis of the ribs secondary to the enlarged intercostal collaterals. Elevated diaphragm, especially in the postoperative setting would mean diaphragmatic paralysis. Eventration of diaphragm also would have the same X-ray picture as that of the diaphragmatic paralysis.

CHEST X-RAY FINDINGS IN SPECIFIC CARDIAC LESIONS

Atrial Septal Defect

Cardiomegaly is usually not a feature. However, if the RV is grossly dilated forming cardiac apex, CTR might be increased. Enlarged right atrial and pulmonary artery shadow are the usual findings. Lung fields show varying degrees of increased PBF. Pulmonary hypertension is not a feature in children. When it occurs in adults, the CXR would show grossly dilated heart and pulmonary arteries.

Ventricular Septal Defect

In the absence of other factors like anemia, cardiomegaly directly correlates with the degree of PBF in all post-tricuspid shunts, which include ventricular septal defect (VSD), aortopulmonary window and patent ductus arteriosus (PDA). Hence, increased CTR is the rule in large defects. Enlarged pulmonary artery and increased PBF are the other findings. If the child develops pulmonary vascular obstructive disease, then the PBF would decrease. This will result in reduction in the LA and LV sizes. Hence, enlarged heart would regress toward normal if the child develops Eisenmenger syndrome. The central pulmonary arteries might still remain dilated. However, the peripheral branches would be reduced in size causing *peripheral pruning* of the pulmonary arteries.

Patent Ductus Arteriosus

In addition to the findings of VSD, ascending aorta and arch could be prominent in large shunts as they too form a part of the left-to-right shunt circuit.

Tetralogy of Fallot

The findings of a classical TOF are absence of cardiomegaly and reduced PBF. Presence of right-sided aortic arch is an important clue. Though *boot-shaped heart* has been traditionally described, it is not consistently seen and is not specific for this diagnosis. Many infants with normal heart too have boot-shaped heart. In pink TOF, the PBF is well-maintained to normal or even higher than normal. Hence, CXR could show mild cardiomegaly with normal to mildly increased PBF.

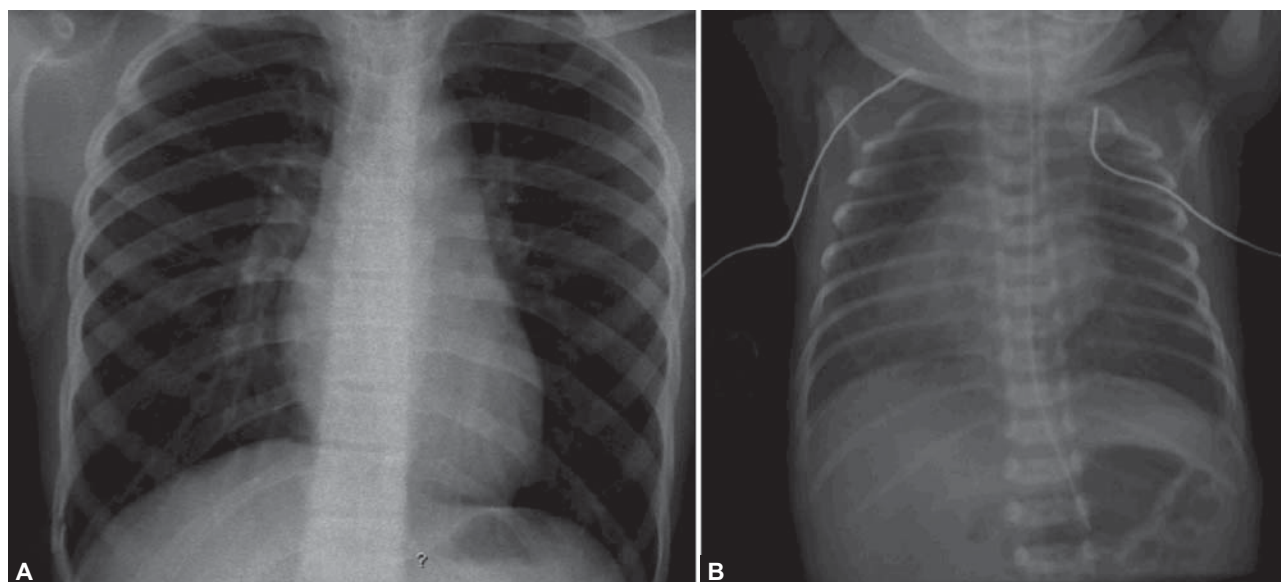
Transposition of Great Arteries

In the early neonatal period, children have cardiomegaly and increased PBF. The *egg-on-side* appearance could be seen in the CXR. In the late neonatal period or older children, PBF and CTR could be normal. If there are additional defects like VSD or PDA, cardiomegaly and increased PBF persist.

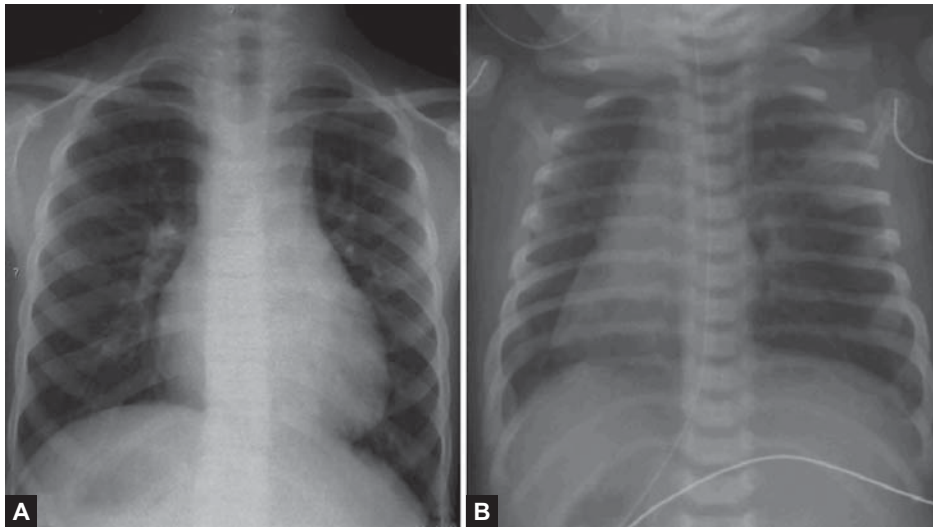
Total Anomalous Pulmonary Venous Drainage

Cardiomegaly is the usual feature. Pulmonary venous hypertension could be noted. In the supracardiac type, *figure-of-eight* appearance has been described. The left superior mediastinal shadow is caused by the vertical vein and dilated SVC causes the corresponding right-sided shadow. However, this finding develops only beyond 3–6 months and should not be relied upon to diagnose this condition, which is a surgical emergency. In obstructed TAPVD (all infradiaphragmatic connections and some of the supracardiac and cardiac types) increased pulmonary venous hypertension causes severe pulmonary edema. This results in ground-glass haze of the lung fields mimicking respiratory distress syndrome.

Figures 1 to 18 depict the common radiological findings in various heart diseases in children.



Figures 1A and B (A) Situs solitus, levocardia. Note the air bubble in the stomach and the bronchial arrangement; (B) There is dextrocardia. However, one should not assume that there is situs inversus. Here too the situs is normal, i.e., solitus



Figures 2A and B (A) The situs is inversus. However, the cardiac shadow is situated more in the left chest with the apex facing left suggestive of dextrocardia. Note that the aortic arch is right sided; (B) Situs inversus with dextrocardia

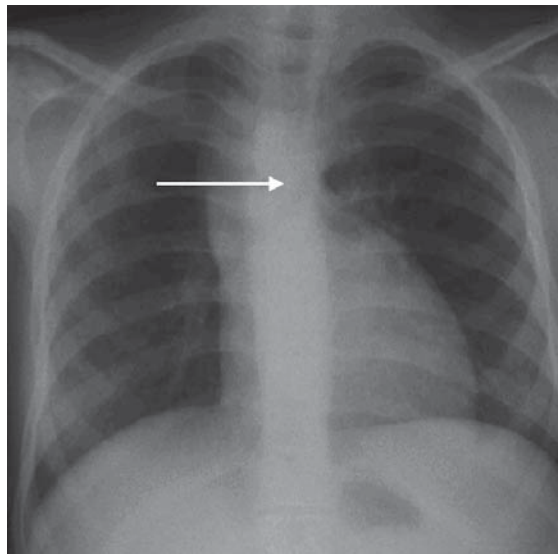
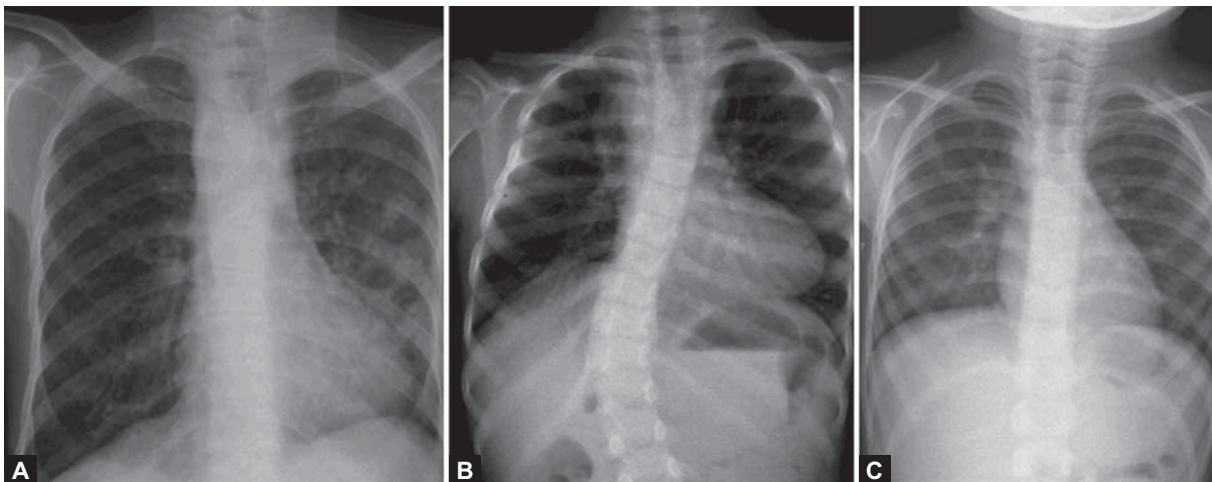
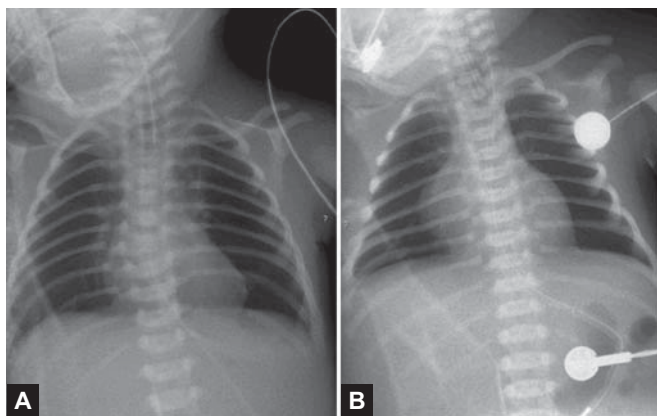


Figure 3 Right aortic arch. The aortic knuckle and the thoracic aorta are obvious in this X-ray. However, the tracheal indentation caused by the aortic arch is more consistent and useful in most of the situations in locating the sidedness of the arch



Figures 4A to C Various examples of right-sided aortic arch. Tracheal indentation is an important and very useful clue



Figures 5A and B These two X-rays are from children who were ventilated for severe cyanosis. They show markedly reduced pulmonary blood flow. Heart diseases causing reduced pulmonary blood flow should be suspected in any child when the degree of systemic desaturation is disproportionate to the lung parenchymal shadows

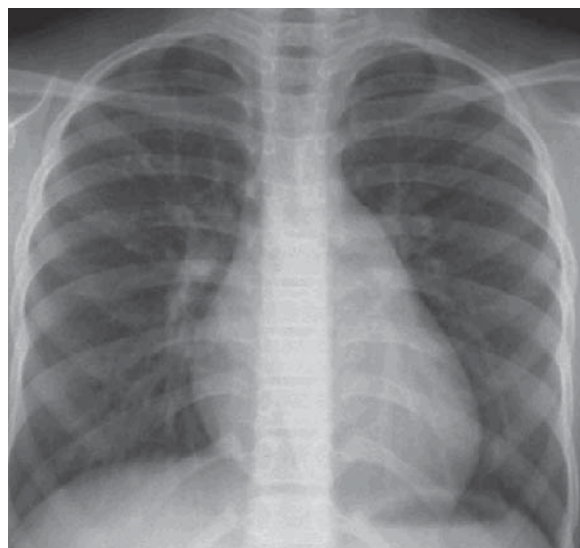


Figure 6 Atrial septal defect. Mild cardiomegaly, prominent right atrium and main pulmonary artery shadows are seen

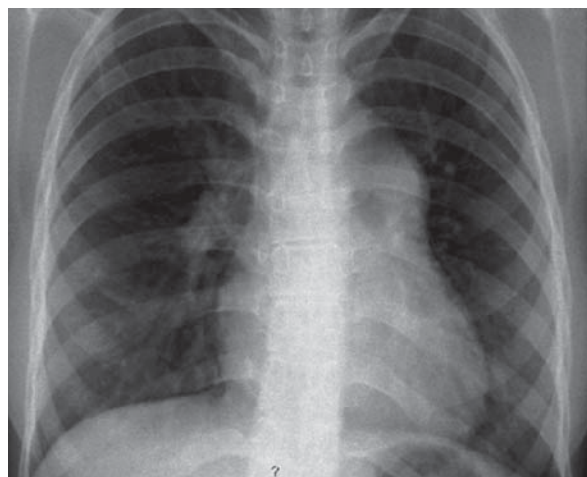


Figure 7 Primary pulmonary hypertension. The findings would mimic atrial septal defect. The main pulmonary artery and branch pulmonary arteries are significantly dilated with minimal or no cardiomegaly



Figure 8 Ventricular septal defect. Cardiomegaly and increased pulmonary blood flow are the findings of a moderate to large defect. Note that the classical description of down and out shifting of apex because of left ventricular dilatation is not always seen in infants

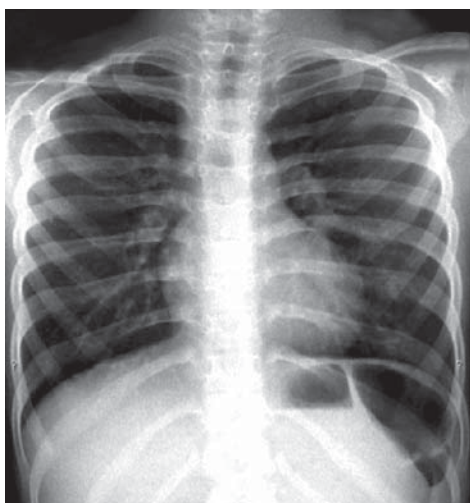


Figure 9 Eisenmenger syndrome. Normal sized heart, prominent hilar pulmonary arteries with pruning of the peripheral vessels

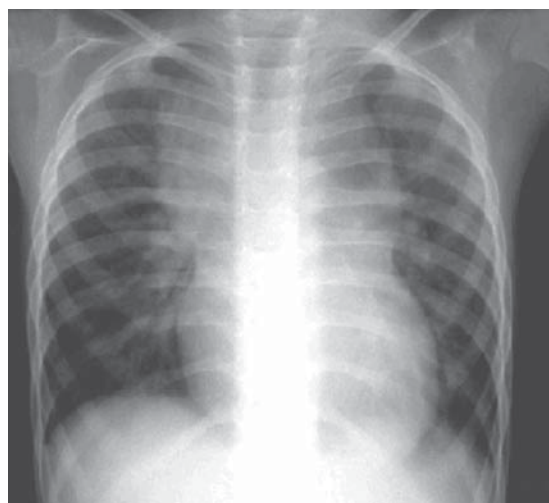
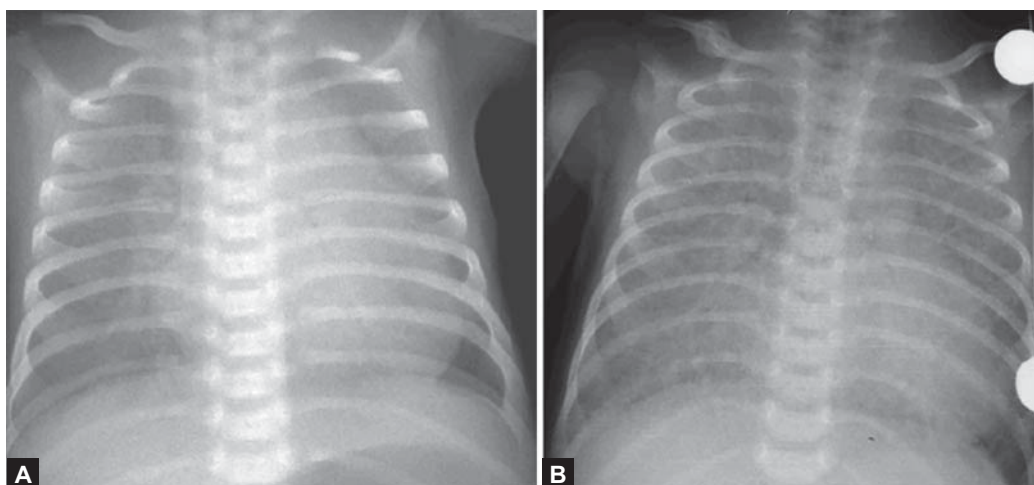


Figure 10 Supracardiac total anomalous pulmonary venous drainage with figure-of-eight appearance



Figures 11A and B Obstructed total anomalous pulmonary venous drainage. Severe pulmonary venous hypertension causes uniform ground glass appearance

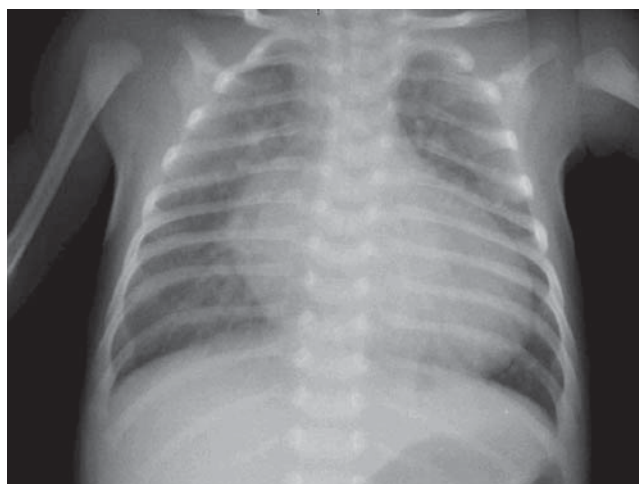


Figure 12 Transposition of great arteries. Cardiomegaly and increased pulmonary blood flow are seen. Absence of thymic shadow results in narrow pedicle and the egg-on-side appearance

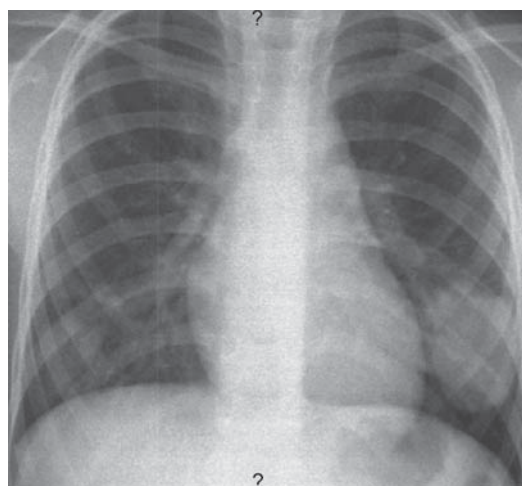


Figure 13 Pulmonary arteriovenous fistula. In a cyanotic child, absence of cardiomegaly and presence of round shadows in the lungs suggests the possibility of this condition

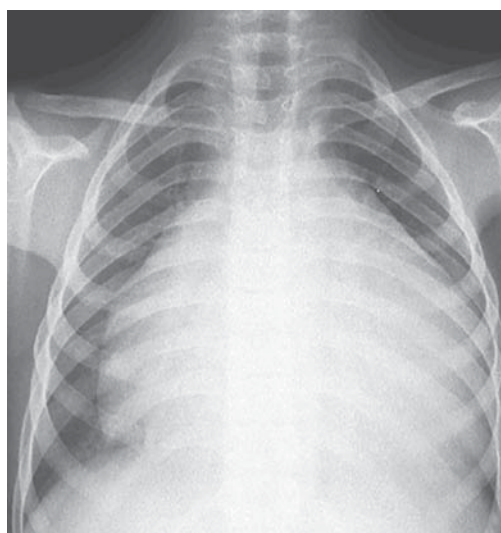
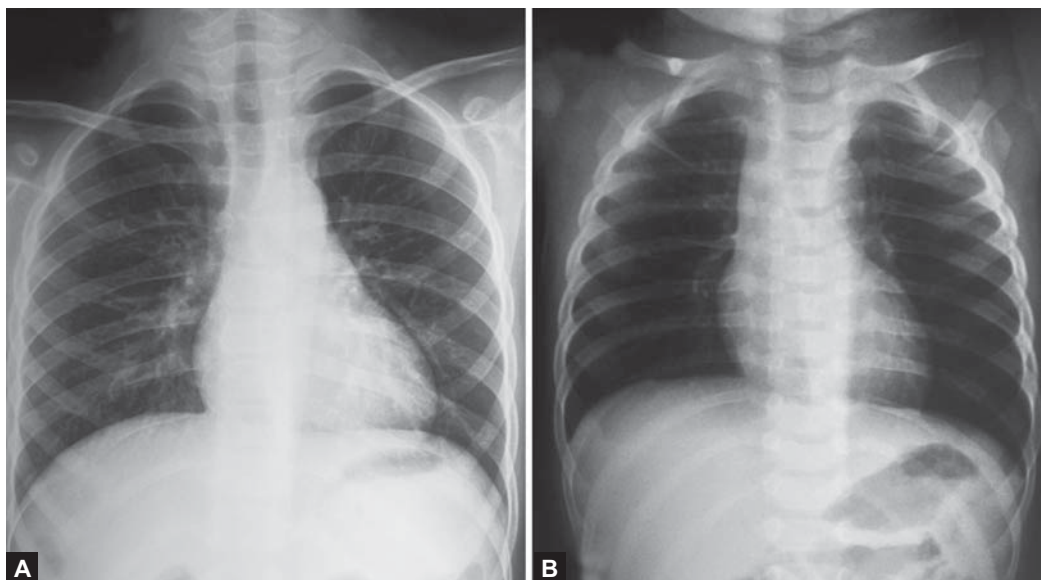


Figure 14 Ebstein's anomaly. Grossly dilated RA and inflow portion of the RV cause cardiomegaly. Other differential diagnoses for this CXR picture are myocarditis/dilated cardiomyopathy and pericardial effusion



Figures 15A and B Tetralogy of Fallot. (A) Pink TOF. Cardiothoracic ratio and pulmonary blood flow are normal; (B) Cyanotic TOF. Heart size is reduced with blackish lung fields suggestive of severely reduced pulmonary blood flow

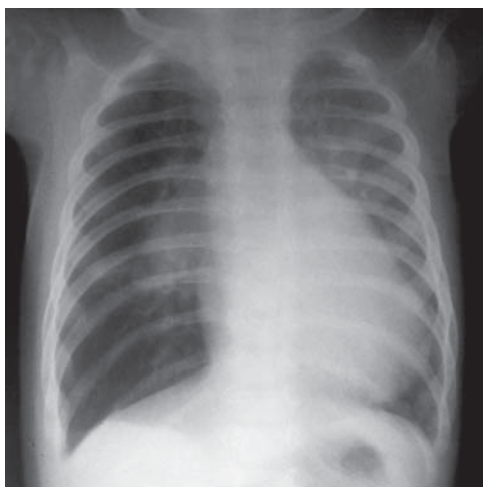


Figure 16 Tetralogy of Fallot with absent pulmonary valve syndrome. Cardiothoracic ratio is increased. MPA and branch pulmonary arteries are grossly dilated

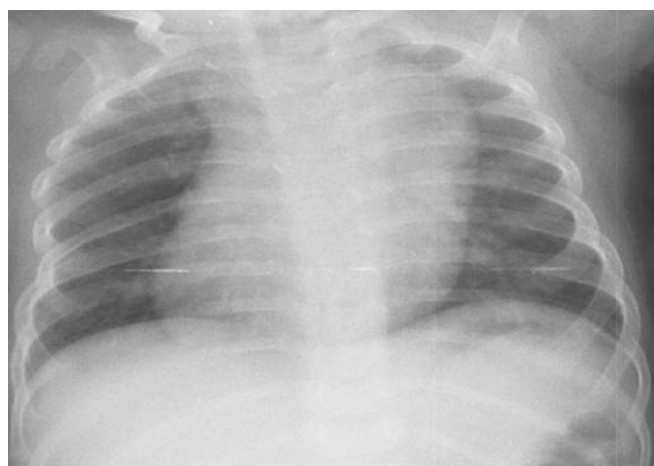


Figure 17 Corrected transposition of great arteries. Situs solitus with dextrocardia. Ascending aorta forms the smooth upper superior mediastinal shadow suggestive of L-shaped aorta

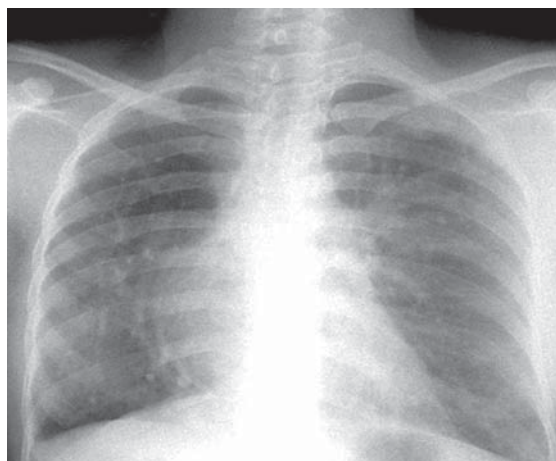


Figure 18 Scimitar syndrome. Note the loss of lung volume in the right lower zone with shift of mediastinum toward right. At times, the anomalously draining scimitar vein could be seen as a curved radiopaque shadow to the right of right border of heart

Chapter 40.9

Echocardiography

Balu Vaidyanathan

FETAL ECHOCARDIOGRAPHY

The availability of fetal echocardiography has provided a unique opportunity to diagnose and understand various forms of congenital heart disease (CHD) from very early gestation. Prenatal diagnosis offers a much wider option for the management of CHD to the expectant family, especially in the setting of limited resource environments.

Indications, Timing and Technique of Fetal Echocardiography

A basic screening of the fetal heart needs to be done in all pregnancies as a part of the mid-trimester anomaly detection scans. A detailed fetal echocardiographic evaluation is indicated in high-risk pregnancies with a greater probability of CHD (Table 1). The optimal timing for fetal echocardiography is between 16 weeks and 20 weeks gestation.

Various clinical societies have their detailed guidelines for conducting fetal echocardiography. This includes evaluation of the fetal lie and position, abdominal situs, four-chamber view, outflow tracts, the three-vessel view, the bicaval view and the evaluation of the ductal and aortic arches. A fetal Doppler evaluation for cardiac rhythm and function completes the study. For the purpose of screening, a combination of four-chamber view and outflow tracts will be adequate to detect most major forms of CHD.

Figures 1 to 3 illustrate the standard views for fetal echocardiography and the common abnormalities detected using these views.

Table 1 Indications for fetal echocardiography

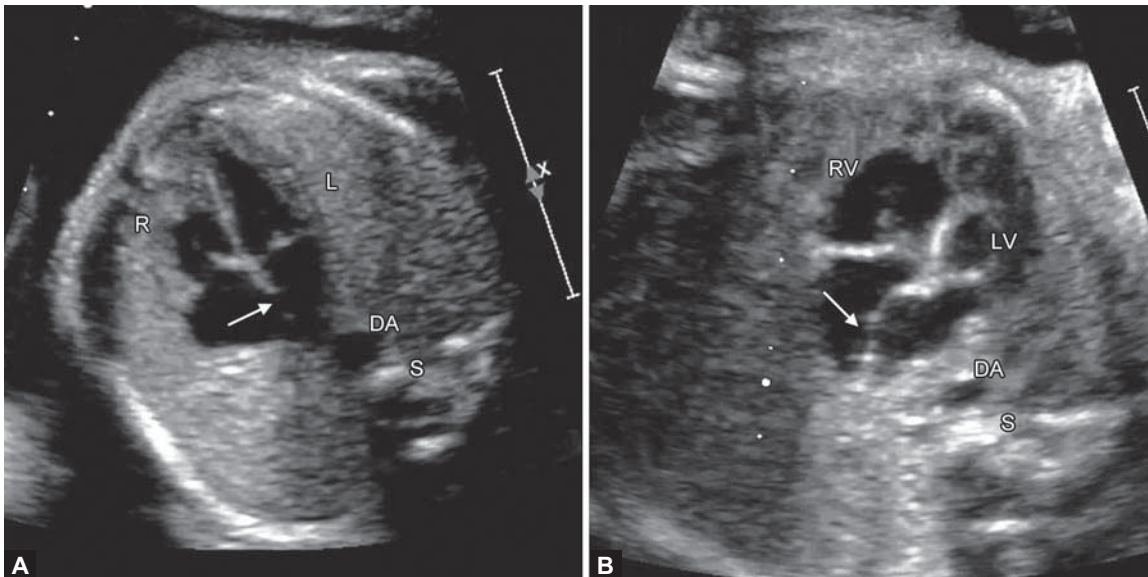
Fetal	Maternal	Familial
1. CHD suspected on screening scans	1. Maternal CHD	1. Previous child with CHD
2. Extracardiac anomalies	2. Teratogen exposure	2. Paternal CHD
3. Chromosomal anomalies	3. Metabolic disorders—Diabetes mellitus	3. Mendelian syndromes
4. Increased first trimester nuchal fold thickness	4. Maternal autoimmune disease	
5. Nonimmune hydrops	5. Intrauterine infections	
6. Irregular heart beat		
7. <i>In vitro</i> fertilization/Intracytoplasmic sperm injection		

Abbreviation: CHD, congenital heart disease.

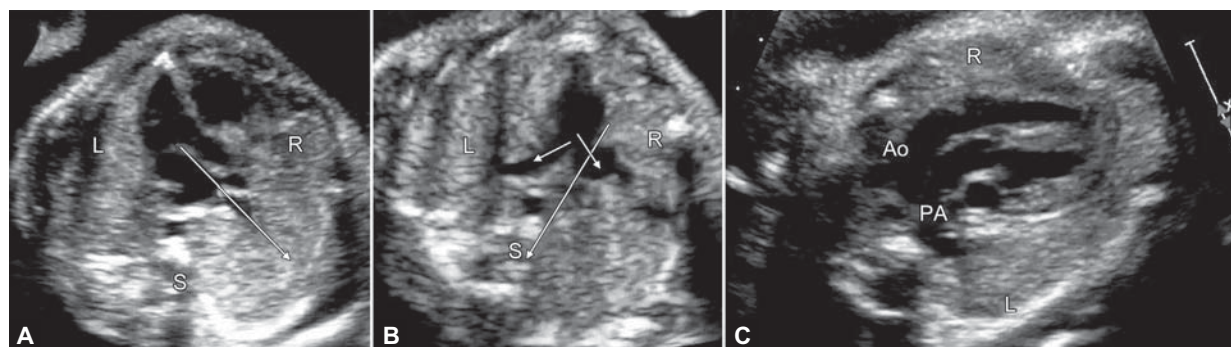
Impact of Prenatal Diagnosis on Management of CHD

The potential impact of prenatal diagnosis on outcomes of fetal CHD depends upon several factors like the complexity of CHD, long-term outcomes after treatment, presence of associated anomalies, psychosocial and economic factors as well as local rules and regulations regarding pregnancy termination. In summary, the following options are available to the family after the diagnosis of fetal CHD:

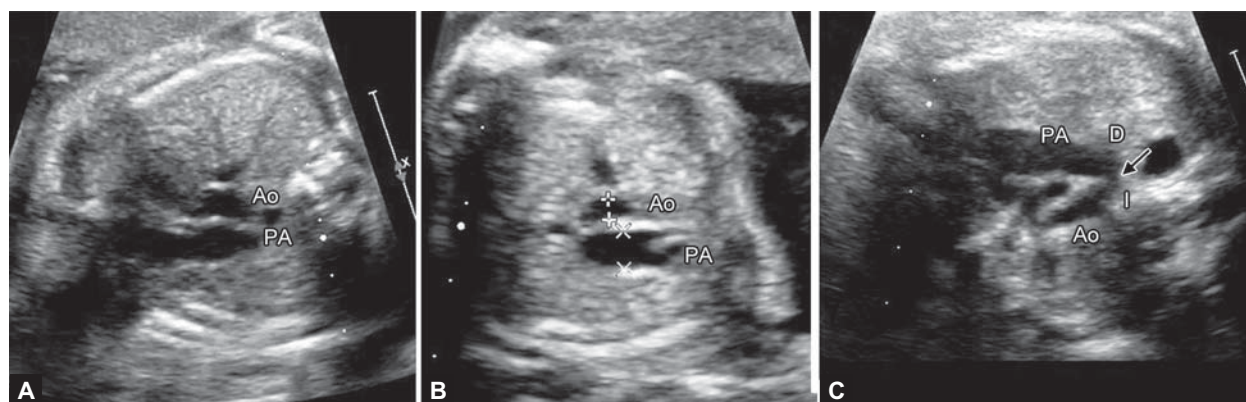
1. *Termination of pregnancy*: An option to be considered and discussed with parents in accordance with the local and regional laws after detection of very complex CHD where only palliative forms of surgery can be offered with guarded or variable long-term outcomes and compromised quality of life.



Figures 1A and B Four-chamber view of fetal heart. Panel A shows a normal four-chamber view of the fetal heart. Note the symmetry of the cardiac chambers. Descending aorta (DA) seen between the left atrium and the spine (S). The arrow points to the patent foramen ovale. Panel B shows a fetal heart with hypoplastic left heart syndrome. The left ventricle (LV) is hypoplastic and the apex of the heart is formed by the right ventricle (RV). The atrial septum (arrow) is bulging toward the right suggesting that the foramen ovale is restrictive or closed



Figures 2A to C Fetal echo: evaluation of outflows. Panel A shows the left ventricular outflow tract (arrow) coursing from the left side toward the right. Panel B shows the direction of the right ventricular outflow tract (bold arrow) coursing from the right of the fetus toward the left and spine (S). The bifurcation of the outflow tract is clearly seen (small arrows). Note that the outflow tracts thus cross each other. Panel C shows the characteristic absence of crossing of outflows with parallel outflow tracts in transposition of the great vessels. The pulmonary artery (PA) is seen arising from the left ventricle while the aorta (Ao) originates from the anterior right ventricle



Figures 3A to C Fetal echo: three-vessel view. Panel A shows a normal three-vessel view with equal sizes of the aorta (Ao) and the pulmonary artery (PA). Panel B shows a relatively small Aorta vis-à-vis pulmonary artery. Panel C shows the significant narrowing of the aorta (black arrow) at the level of Isthmus (I). The arterial duct is also shown (D). Panel B and C characterize the typical findings in fetal coarctation of aorta

2. *Planned delivery and perinatal cardiac care:* This is applicable for CHDs that are potentially lethal in the neonatal period without appropriate specialist intervention and treatment (e.g., transposition of the great arteries, other ductus dependent conditions) which offers a possibility of favorable long-term outcomes with reasonable quality of life.
3. *Transplacental therapy:* This is offered for fetuses with tachyarrhythmia and bradyarrhythmias including complete heart block with excellent results in current era.
4. *Fetal interventions:* At present the scope of fetal cardiac interventions is limited to obstructive lesions of outflow tracts, especially aortic stenosis.

ECHOCARDIOGRAPHY IN THE NEONATE

The definitive diagnosis of CHD at the bedside is feasible by echocardiography. Besides a detailed anatomic evaluation of CHD, echocardiography also permits comprehensive *functional and hemodynamic evaluation* of the heart such as degree or severity of obstructions, regurgitations, contractility besides cardiac output. Indications for neonatal echocardiography are listed in **Box 1**.

Protocol for Neonatal Echocardiography

A sequential chamber analysis using a combination of echocardiographic views is recommended. A broad guideline only is

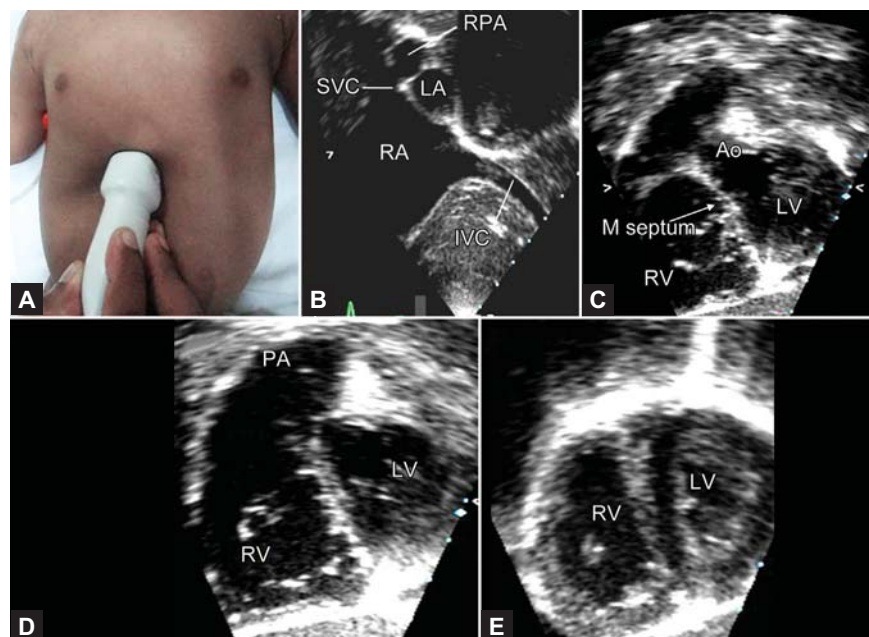
BOX 1 Indications for neonatal echocardiography

- Whenever CHD is suspected based on clinical evaluation (presence of cardiac murmur, cyanosis, discrepant pulses or any unexplained circulatory failure and shock)
- Failed routine neonatal pulse oximetry screening test
- All those with genetic syndromes or extracardiac anomalies commonly associated with CHD (e.g., Trisomy 21, 22q deletion syndrome, VACTERL association, etc.).

given and for detailed protocol for echocardiography the interested reader may refer to the suggested references. The following steps are used to identify:

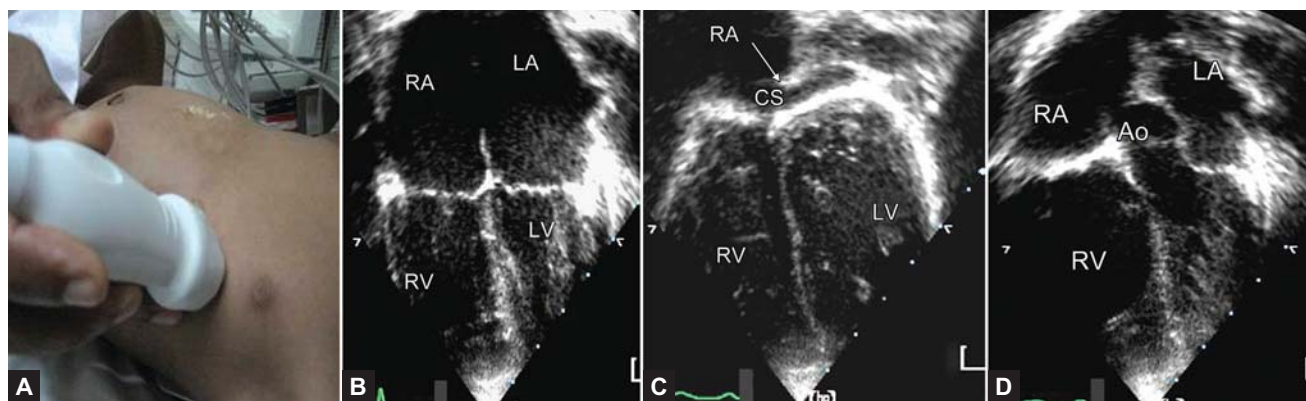
1. The liver and splenic positions in the abdomen and atrial situs and atrial arrangement.
2. Ventricular morphology and atrioventricular connection (concordance).
3. Identification of great vessels and ventriculoarterial concordance.
4. Associated abnormalities and assessment of their severity.

The following views or windows are commonly employed to gather information during echocardiographic evaluation: (1) subxiphoid: (i) long and (ii) short axis views; (2) four-chamber view; (3) parasternal, (i) long and (ii) short axis views; (4) ductal view (high parasternal short axis view); and (5) suprasternal view.



Figures 4A to E Subxiphoid view evaluation. Panel A shows the position of the transducer in subxiphoid view evaluation. Note that the transducer is held vertical with pointer facing toward the feet of the patient. Panels B to E show various structures seen on sweeping the transducer from right to left on subxiphoid short axis sweep. Starting from atria, atrial septum and systemic veins (Panel B), one can visualize the various components of the ventricular septum from membranous (Panel C, bold arrow), infundibular (Panel D) and apical (Panel E)

Abbreviations: RA, right atrium; LA, left atrium; SVC, superior vena cava; IVC, inferior vena cava; RPA, right pulmonary artery; RV, right ventricle; LV, left ventricle; RVOT, right ventricular outflow tract; PA, pulmonary artery.



Figures 5A to D Four-chamber view. Panel A shows the position of the transducer in this view. The transducer is placed in the cardiac apex with pointer facing to the left. Sweeps are made in the anteroposterior plane to visualize the cardiac chambers and valves (Panel B), coronary sinus by caudal tilt (Panel C, arrow) and left ventricular outflow tract by cranial tilt (panel D)

Abbreviations: RA, right atrium; LA, left atrium; RV, right ventricle; LV, left ventricle; CS, coronary sinus; Ao, aorta.

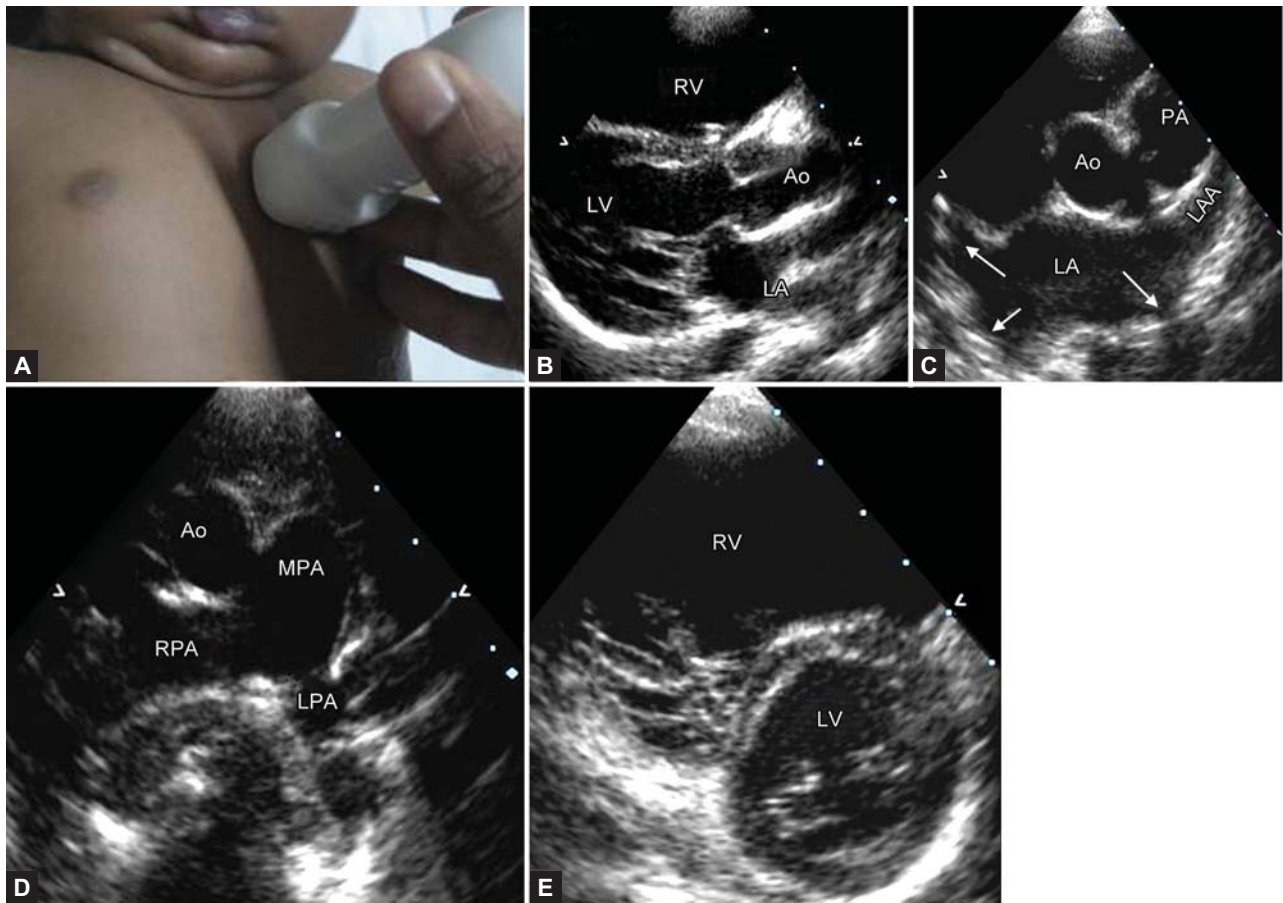
- In the subcostal approach, various structures are imaged by sweeping the transducer in the cephalocaudal plane (long axis) or right to left sweep in short axis,
- The subxiphoid views permit detailed evaluation of situs, position of heart and its connections, atrial and ventricular septum and atrioventricular valves,
- The four-chamber and the parasternal views provide additional information about ventricular function, valves and outflows,
- The ductal view (high parasternal short axis view) for the PDA, and
- Suprasternal view for the evaluation of aortic arch.

In a sick neonate, the echocardiographic evaluation may have to be limited to the most essential views taking care that the hemodynamic status of the patient is not compromised during the study (especially suprasternal views in a ventilated neonate). **Figures 4 to 8** illustrate the common echocardiographic views and the corresponding images of the heart obtained in each view.

Standard principles for image optimization, Doppler evaluation and measurements need to be followed.

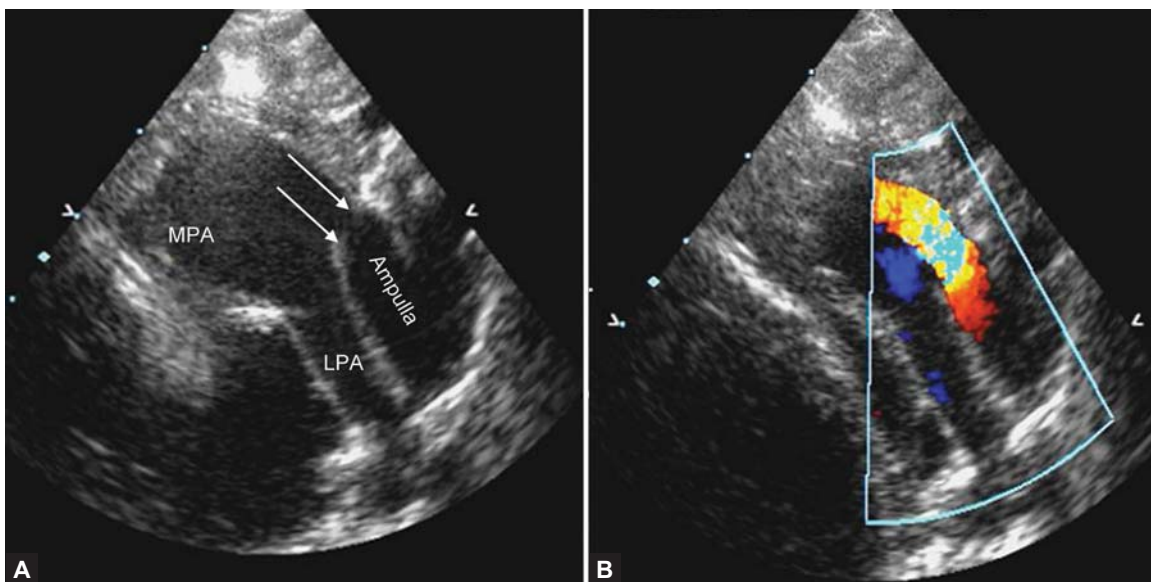
Functional Echocardiography

This approach utilizes a combination of two-dimensional and M-Mode imaging and Doppler (continuous wave, pulse wave



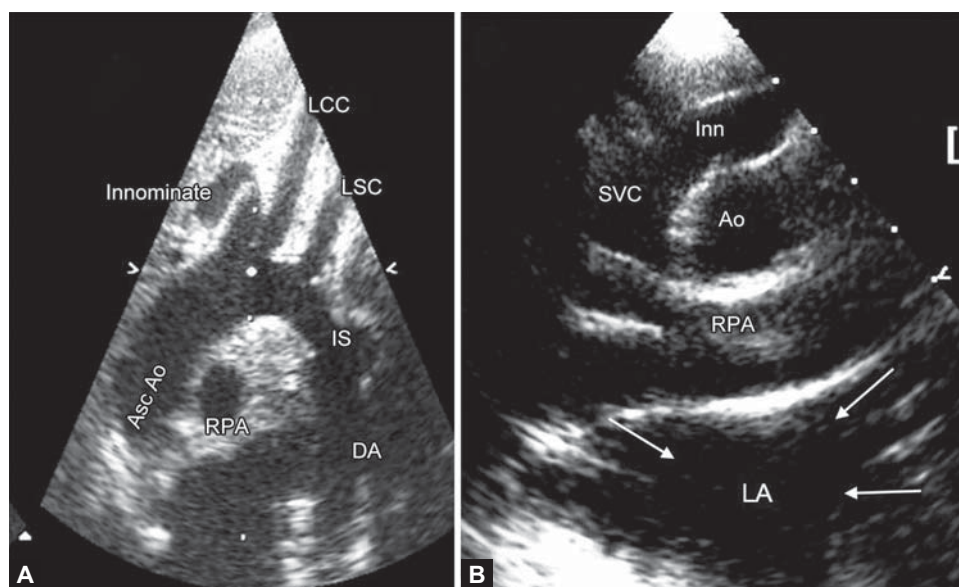
Figures 6A to E Parasternal views. Panel A shows the position of transducer in these views. In the parasternal long axis view, the transducer is placed along the left side of sternum with pointer facing toward right shoulder. Rotating the transducer through 90° with pointer facing left shoulder gives the short axis view. Panel B shows the parasternal long axis image of the heart showing the left ventricular outflow tract, mitral valve and left atrium. Panel C is a short axis view of the semilunar valves and coronaries. The left atrium with the pulmonary veins (arrows) and appendage are seen posterior to aorta. Panel D is a short axis view showing the bifurcation of the pulmonary arteries. Panel E shows a short axis view of the left ventricle and mitral valve obtained by tilting the transducer caudally

Abbreviations: LA, left atrium; Ao, aorta; RV, right ventricle; LV, left ventricle; PA, pulmonary artery; LAA, left atrial appendage; MPA, RPA, LPA, main, right and left pulmonary artery.



Figures 7A and B High parasternal (ductal) view. This view is obtained by keeping the transducer in the first left intercostal space with transducer facing cranially. Panel A shows the anatomy of the patent ductus arteriosus (PDA). The arrows indicate the pulmonary end of the PDA, which is typically the narrowest portion. The diameter of the PDA is measured at this level. The duct ampulla is well profiled. Panel B shows color Doppler flow evaluation of the PDA with a left-to-right flow

Abbreviations: MPA, main pulmonary artery; LPA, left pulmonary artery.



Figures 8A and B Suprasternal view. This is obtained by keeping the transducer in the suprasternal notch. Panel A shows the long-axis image imaging the aortic arch and its branches. Panel B shows a short axis suprasternal view by rotating the transducer to the right by 90°. This view is excellent for imaging the superior vena cava and its innominate connection and the pulmonary arteries. A caudal tilt from this position shows the left atrium with all the pulmonary veins draining into it (arrows, Crab view)

Abbreviations: LCC, left common carotid; LSC, left subclavian; Inn, innominate vein; RPA, right pulmonary artery; LA, left atrium; Ao, aorta; Is, Isthmus; DA, descending aorta.

and color) for the evaluation of cardiac function. Evaluation of cardiac output is feasible through measurement of either left or right ventricular outputs or by superior vena cava (SVC) flow. Functional echocardiography is extremely valuable in hemodynamic assessment of PDA and its significance; evaluation of pulmonary artery pressures and RV function in infants with persistent pulmonary hypertension of the newborn (PPHN); and evaluation of shock states in neonates and infants.

Pitfalls, Limitations and Lesions often Overlooked

Echocardiography is a subjective tool and the quality of the study is influenced by several factors. Equipment quality and expertise of the echocardiographer are primary determinants of accuracy in reporting. The patient related factors and echo windows significantly affect the study. In very sick neonates on ventilator, echo windows maybe suboptimal due to hyperinflated lungs and the study may have to be truncated to get basic information.

Some of the common critical CHDs that are often overlooked include anomalous pulmonary venous connections, coarctation of aorta and coronary anomalies. Clues for anomalous pulmonary venous connections include significant enlargement of right-sided chambers, relatively small left atrium, severe pulmonary hypertension and an atrial level communication shunting exclusively right-to-left. In such cases, a careful search for the common pulmonary vein chamber and its drainage site is required. Exclusion of coarctation is mandatory in any neonate with unexplained shock and this is feasible through a thorough evaluation of the aortic arch using the suprasternal view. In young infants with left ventricular dysfunction, coronary anomalies like anomalous left coronary artery from the pulmonary artery (ALCAPA) must be carefully looked for. Presence of wall motion abnormalities and scarred papillary muscles should prompt a very close evaluation with color Doppler of the coronaries using the parasternal short axis view.

IN A NUTSHELL

1. Echocardiography is the gold standard for bedside diagnosis of CHD.
2. Prenatal diagnosis of CHD is feasible using antenatal ultrasound screening; basic evaluation includes the four-chamber view, outflow tracts and the three-vessel view.
3. Prenatal diagnosis can significantly impact the management of severe forms of CHD in the current era.
4. Bedside echocardiography is the definitive method to exclude CHD in the newborn baby.
5. A standard protocol for evaluation the heart in a segmental manner needs to be followed for the conduct of echocardiography.
6. Functional echocardiography permits a detailed evaluation of the underlying hemodynamic status and this can have a significant impact on management of a sick neonate in the NICU (especially in treatment of PDA in the preterm infant).
7. Clinicians performing echocardiography in the neonate needs to be aware of the pitfalls and the common lesions which may be overlooked.
8. Recent data on neonatologists performing echocardiography have shown high sensitivity and specificity for detection of CHD and cardiac functional assessment.
9. Echocardiography has the potential to significantly impact early diagnosis of CHD and hemodynamic monitoring of sick infants in the NICU in the near future.
10. There is a pressing need for formal training and accreditation programs in neonatologist performed echocardiography, in collaboration with pediatric cardiologists.

MORE ON THIS TOPIC

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Chapter 40.10

Cardiac Catheterization

Duraisamy Balaguru

Cardiac catheterization is an invasive modality where small catheters are inserted via vein and artery respectively to obtain direct pressure and oxygen saturation measurement. Injection of radiologic contrast dye provides angiograms for anatomic and flow details. From the oxygen saturation and pressure measurements, various calculations can be made including cardiac output, estimates of pulmonary blood flow and vascular resistance, intracardiac shunts and valve area. Technologic advances including balloon catheters, stents, occlusion devices and valves enable transcatheter treatment of cardiovascular defects. Recent developments enable three-dimensional construction of images from rotational angiography. Cardiac magnetic resonance imaging (MRI) and computed tomography (CT) scans provide alternative noninvasive methods of imaging to aid diagnosis and management of congenital heart disease in children.

CARDIAC CATHETERIZATION

Indications

- Diagnosis of cardiac and extracardiac vascular defects by angiography and assessment of cardiac function by measurement of cardiac output, intracardiac shunts, pulmonary vascular resistances and valve area.
- Pulmonary vasoreactivity testing in patients with pulmonary hypertension with or without congenital heart defects.
- Transcatheter treatment of cardiac and extracardiac defects—balloon atrial septostomy, balloon valvuloplasty, balloon angioplasties, stent therapy, closure of congenital heart defects and transcatheter valve placements. Transcatheter therapy has become first-line management in suitable patients for the following conditions: Valvar stenosis [pulmonary stenosis, aortic stenosis (PS, AS)], coarctation, patent ductus arteriosus (PDA), atrial septal defect (ASD), ventricular septal defect (VSD) and extracardiac collateral vessels. These procedures are briefly reviewed below.

Even though indications for cardiac catheterization for diagnostic purpose only have diminished since the advent of echocardiography, cardiac MRI and CT scans, approximately 40–45% of the procedures in a catheterization laboratory constitute diagnostic catheterizations.

Vascular Access

Establishing access to the vascular system—venous, arterial or both—is the first step in cardiac catheterization. Standard approach for children includes percutaneous Seldinger technique via femoral vein and femoral artery. Additional options for venous access include umbilical vein in neonates, subclavian and internal jugular veins in all age groups. Additional options for arterial access include umbilical artery in neonates. Radial, brachial, axillary and carotid artery may be used in other age groups under special circumstances. Carotid artery access is obtained usually by a surgical cut-down procedure. Vascular access may be difficult in patients with small or stenotic vessels from prior catheterizations, additional guidance with Doppler or ultrasonography may increase the success of obtaining vascular access.

TRANSCATHETER TREATMENT

Balloon Atrial Septostomy

Balloon atrial septostomy is performed in newborns or infants, to enlarge the atrial level communication between right and left atria. A balloon catheter is introduced from the femoral or umbilical vein, advanced across patent foramen ovale (PFO) to left atrium (LA). The balloon is then inflated in LA (**Fig. 1**) and pulled across the PFO to right atrium, creating a larger atrial level opening. Indication for this procedure includes (i) dextrotransposition of great arteries in a newborn who has inadequate mixing, (ii) decompression of right atrium in tricuspid atresia and (iii) decompression of left atrium in mitral atresia and related disorders. This procedure is highly effective in newborns. But, may be more difficult in older infants due to thickening of the atrial septum with age where blade atrial septostomy or static-balloon atrial septoplasty is performed with or without stent placement.

Balloon Valvuloplasty

Isolated, moderate to severe pulmonary or aortic valve stenosis is the common indication for this procedure in children. Congenital mitral stenosis and tricuspid stenosis requiring balloon valvuloplasty are rare. Rheumatic mitral stenosis is amenable to this procedure as well. However, significant rheumatic mitral stenosis is more common in adolescents and adults than young children. Presence of moderate or severe valvar regurgitation is a contraindication for the procedure.

Procedure involves placing an appropriate size balloon across the stenotic valve and inflating to a 2–4 atmospheric pressures until the waist in the balloon is obliterated. Results of balloon pulmonary valvuloplasty (**Fig. 2**) are excellent with low recurrence rate. Pulmonary regurgitation induced by balloon procedure is minimal and well tolerated. On the contrary, balloon aortic valvuloplasty (**Fig. 3**) has relatively poorer results with higher rate of recurrence. Aortic regurgitation induced by balloon procedure may be poorly tolerated especially if it is severe. For isolated pulmonary stenosis and aortic stenosis, balloon valvuloplasty is considered the first choice of treatment.

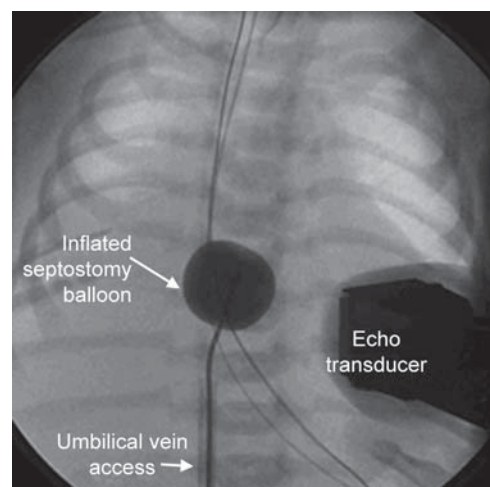


Figure 1 Balloon atrial septostomy in a newborn. Image shows Rashkind's septostomy catheter is inflated in the left atrium using dilute contrast. This balloon will be pulled across the patent foramen ovale using fluoroscopy and echocardiographic guidance (Echo transducer is held by a technician at the chest to provide additional guidance during the procedure). Umbilical venous access was used in this 1-day-old newborn with transposition of great arteries

Balloon Angioplasty and Stents

Coarctation of aorta (except during infancy) (**Figs 4 and 5**) and pulmonary artery stenosis (**Figs 6A to C**) are indications. Balloon angioplasty can also be applied to stenosis of other vessels such as superior vena cava (SVC), inferior vena cava (IVC) and surgical conduits. These procedures have been highly successful with technologic developments in balloon design. Restenosis develops in approximately ~30% of children who undergo successful balloon angioplasty. Placement of stents prevents or reduces the restenosis rate. However, since currently-available stents do not grow with the child, stent placement is limited to older children or to children with surgical conduits that are planned for replacement at a future surgery. Balloon angioplasty and stent procedures have helped to prolong the longevity of surgically placed conduits.

Patent Ductus Arteriosus Closure

Transcatheter closure is the first-line therapy for PDA. Various devices including Gianturco coils (**Figs 7A and B**), and Amplatzer

duct occluders (St Jude Medical, Minneapolis, MN, USA) and Nit-Occlud device (PFM medical, Koln, Germany) are some of the transcatheter device options. Excellent results are achieved using transcatheter closure of PDA. Transcatheter technique is not suitable for preterm babies and small infants at this time, though this is evolving. When transcatheter technique is not suitable either due to PDA size/anatomy or patient size, surgical ligation is the option. Surgical ligation is performed either by thoracotomy or using thoracoscope (Video-assisted thoracoscopic surgery). Video-assisted thoracoscopic surgery for PDA closure is available in some centers for children of all sizes, including premature infants down to 600 g.

Atrial Septal Defect Closure

Only secundum type ASD that is centrally-placed with adequate rim of tissue around the defect is suitable for transcatheter device closure. Primum ASD and sinus venosus type ASDs need surgical repair when closure is indicated. Several transcatheter ASD

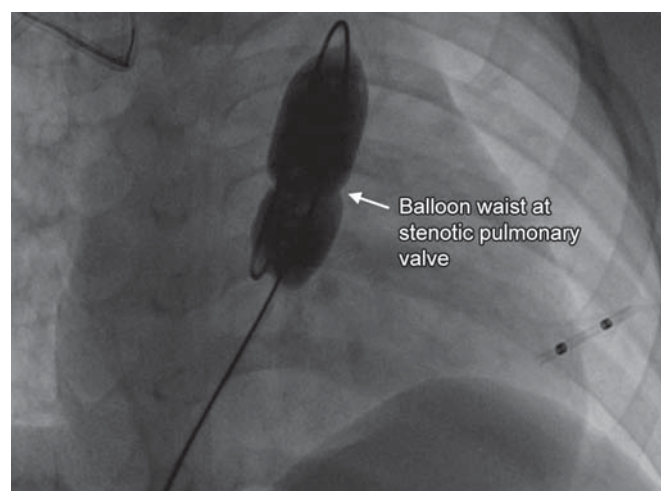


Figure 2 Balloon pulmonary valvuloplasty. Still image during balloon inflation showing the waist in the balloon at the level of pulmonary valve. This waist will be obliterated with full inflation of the balloon. 10 mm calibration marker is on the skin over left chest. Femoral venous access is used for the procedure

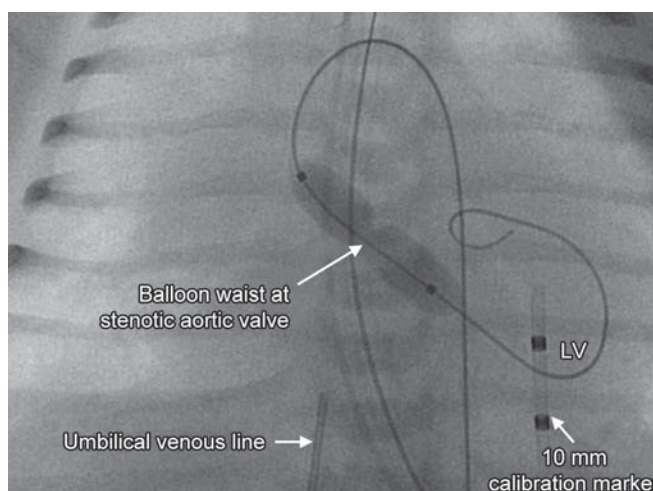
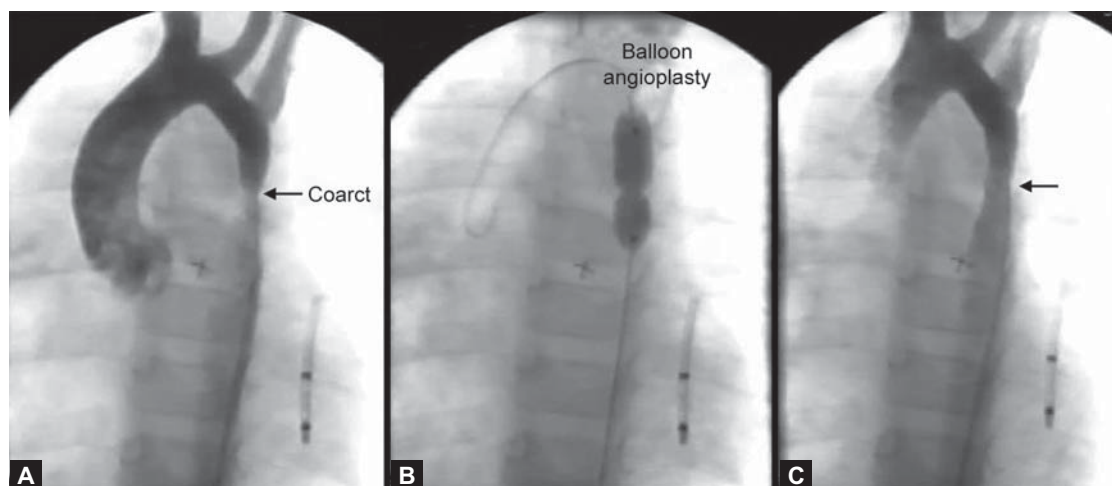
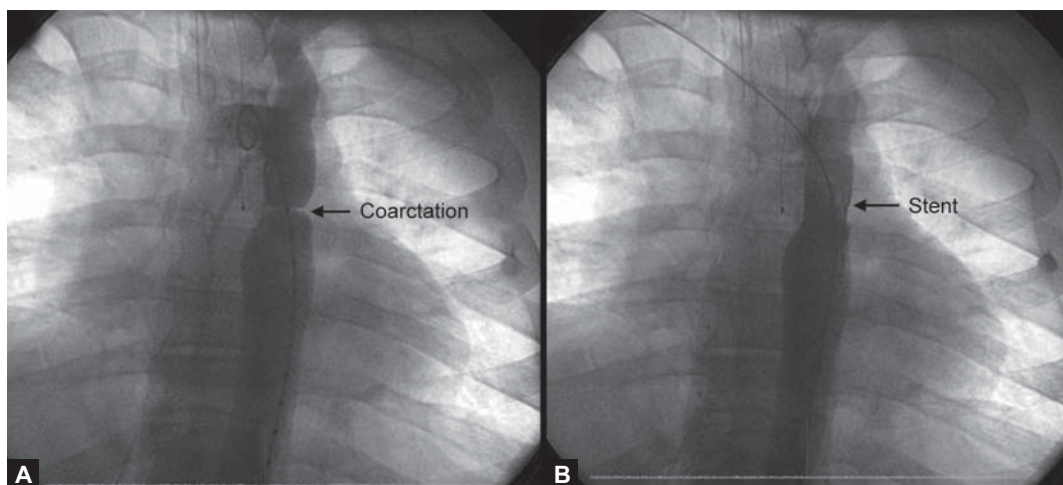


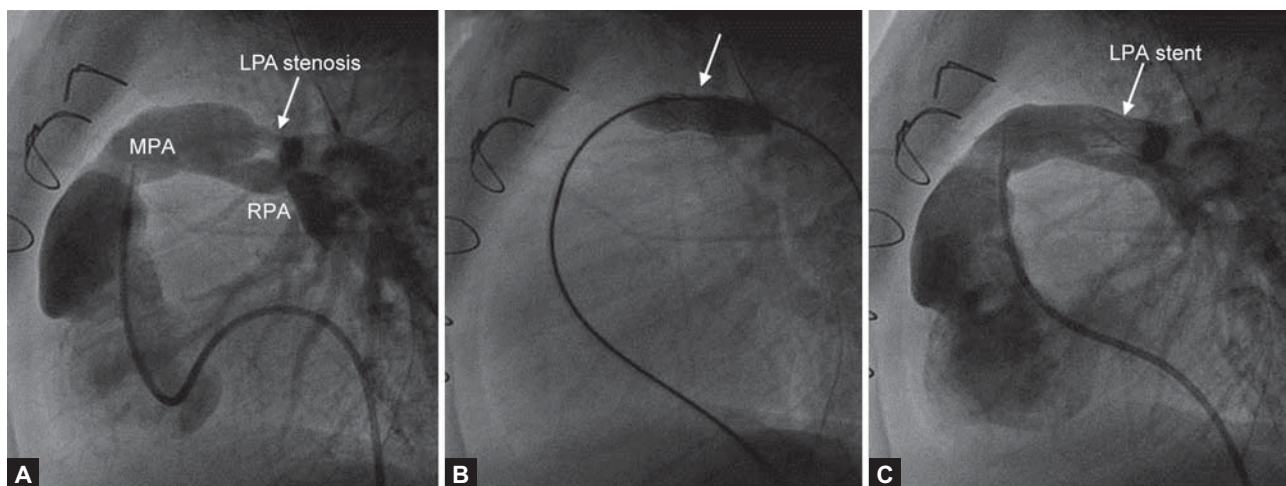
Figure 3 Balloon aortic valvuloplasty in a newborn with critical aortic stenosis. Still frame during balloon inflation across the aortic valve. Waist in the balloon is at the level of stenotic aortic valve. Catheter is advanced from femoral artery over a guidewire whose tip is curled up in left ventricle (LV). Umbilical venous line is used for infusions



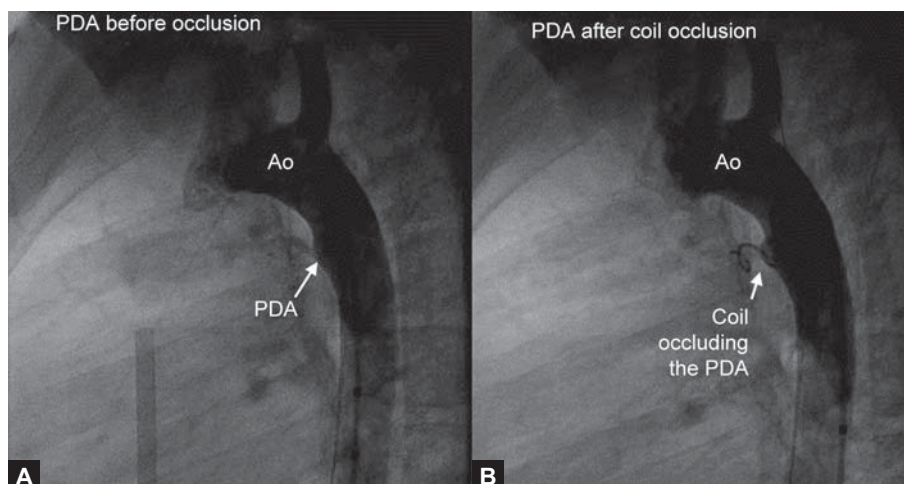
Figures 4A to C Balloon angioplasty of coarctation. Panel A—Aortic root angiogram shows coarctation (Coarct); Panel B shows balloon inflated across the coarctation segment and Panel C shows good improvement in diameter of the coarctation segment



Figures 5A and B Stent angioplasty of coarctation of aorta in a teenager. Panel A shows PA view of aortogram with a discrete coarctation; Panel B shows the same segment with significant increase in size after stent placement



Figures 6A to C Lateral view images of MPA angiograms illustrating stent placement for left pulmonary artery (LPA) stenosis in a 4-year-old girl after tetralogy of Fallot repair. Panel A shows severe stenosis of origin of LPA; Panel B shows the inflation of balloon with stent mounted on it and Panel C shows MPA angiogram after stent placement. Now, LPA origin is widely open
Abbreviations: MPA, main pulmonary artery; LPA, left pulmonary artery; RPA, right pulmonary artery.

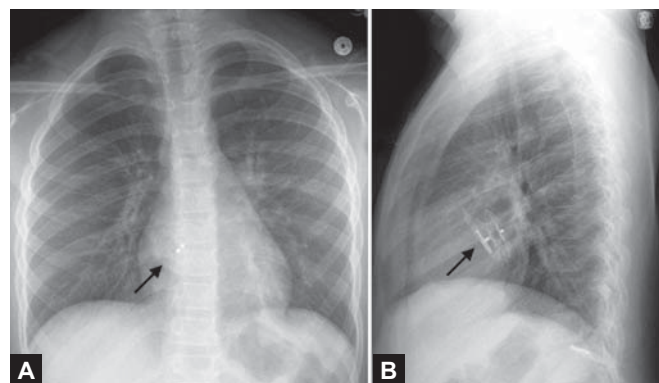


Figures 7A and B Still frames of lateral view of aortic arch (AA) angiograms. Panel A shows a small patent ductus arteriosus (PDA) before closure and Panel B shows a coil delivered by catheterization, occluding the patent ductus arteriosus. No residual shunt is noted

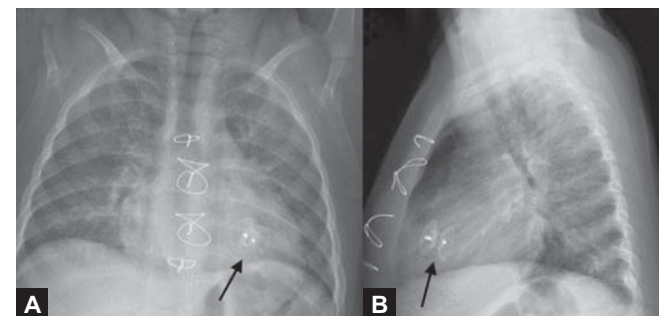
devices are available. Amplatzer septal occluder (St Jude Medical) and Helex® device (WL Gore, Flagstaff, Arizona, AZ, USA) are the popular devices. There are several other devices under development or in clinical trials. In principle, all ASD devices have a waist connecting the two discs. The device is collapsed and loaded into the delivery catheter. The device expands upon delivery inside the heart. The waist portion is placed in the ASD, with the two discs holding the device in place after release. Chest X-ray of a patient with Amplatzer septal occluder is shown in **Figures 8A and B**. Patient selection is important for successful device closure and in preventing complications after device placement. Residual defects occurs after the procedure; majority of them spontaneously close 6 months to 1 year after the procedure.

Ventricular Septal Defect Closure

There are several types of VSDs. Muscular type VSD located sufficiently away from nearby valves is amenable to transcatheter device closure. **Figures 9A and B** shows chest X-ray of an infant who underwent closure of apical muscular VSD using Amplatzer muscular VSD device. Device for membranous VSD closure is in clinical trial at this time. VSD devices are designed similar to ASD devices with wider waist to accommodate for thicker ventricular septum. These are delivered either from femoral venous access or internal jugular venous access. When percutaneous approach is difficult, this procedure is performed by a hybrid approach where a sternotomy is performed and the device is placed through a delivery sheath inserted through the RV free wall of the beating



Figures 8A and B Chest X-ray in PA and lateral views in a patient who underwent transcatheter closure of ASD using Amplatzer septal occluder (black arrows). Device is easier to appreciate in lateral view (Panel B) where the two discs and central waist are recognizable
Abbreviation: ASD, atrial septal defect.



Figures 9A and B Chest X-ray images of a 2-year-old girl who underwent transcatheter closure of apical ventricular septal defect and atrial septal defect using respective Amplatzer devices
Abbreviations: ASD, atrial septal defect; VSD, ventricular septal device.

heart. Hybrid approach avoids an open heart surgery and is a preferred method for small infants in whom percutaneous approach is riskier due to higher incidence of myocardial perforation.

Transcatheter Valve Implantation

Transcatheter pulmonary valve implantation is performed in patients who have undergone prior cardiac surgery for tetralogy of Fallot, pulmonary atresia (PA) or double outlet right ventricle (DORV) with placement of right ventricle (RV)-PA conduit. Current commercially available valve (Melody® Valve; Medtronic Inc. Minneapolis, MN, USA) is a bovine jugular venous valve sutured inside a stent. The stent is then, mounted on a balloon and deployed in RV-PA conduit in pulmonary valve position. Native pulmonary valve annulus is considered unsuitable for transcatheter valve implantation at this time. Transcatheter aortic valve implantations are being performed under clinical trials for elderly adults with aortic stenosis. These transcatheter aortic valves are not suitable for children at this time.

OTHER ADVANCED IMAGING METHODS

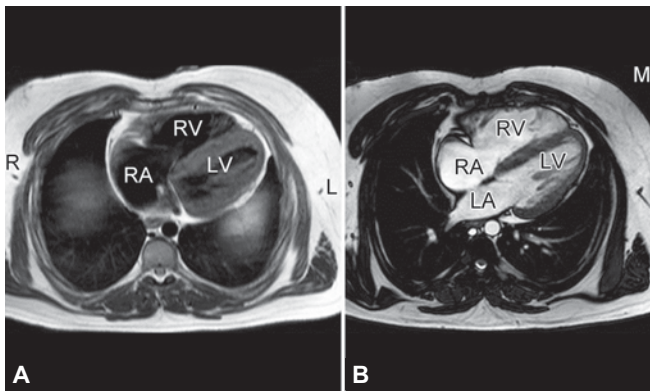
Cardiac Magnetic Resonance Imaging

Cardiac MRI is uniquely suited for certain indications such as pulmonary venous return, vascular ring and related anomalies, aortic arch and its branches and similar lesions when they are difficult to define using echocardiography. Intracardiac anatomy is obtained with good tissue characterization (e.g., tumors) and reproducible volume measures, flow characteristics and flow measurements. For example, patients are followed after repair of tetralogy of Fallot with serial MRI at 3–5-year intervals, to measure RV and pulmonary regurgitation volume to determine optimal time for pulmonary valve implantation. **Figures 10A and B** show axial images of a teenager after tetralogy of Fallot repair and mild right ventricular dilatation. Contrast enhanced MRI using Gadolinium provide MR angiography providing functional anatomy, myocardial viability, inflammation and estimation of iron stores. **Figures 11A to C** show a three-dimensional reconstruction of a double-aortic arch.

Limitations of cardiac MRI include lack of widespread availability of the facility or expertise to perform the imaging, need for sedation or general anesthesia in infants and children, prolonged scan times (may exceed 1–2 hours) in sick children and incompatibility of ferromagnetic prosthetic implants in or around the heart such as pacemakers.

Cardiac Computed Tomography

Cardiac CT provides images comparable to cardiac MRI and provides ability to perform three-dimensional reconstructions (**Fig. 12**). However, cardiac CT requires contrast injection to delineate cardiac chambers and blood vessels. Furthermore, cardiac CT uses X-ray causing radiation exposure to the patient. Advantages over cardiac MRI are that acquisition of images is much faster taking a few minutes and when there are ferromagnetic prosthetic implants in the patient. Timing of contrast injection and image acquisition is important. Additional advantage is ability to reconstruct noncardiac structures that will have significant implications in managing the patients. **Figures 13A and B** show images from a 10-month-old child with anomalous origin of left pulmonary artery from right pulmonary artery (the so-called pulmonary artery sling). In this condition, usually there are associated tracheal and bronchial abnormalities as shown by accessory right bronchus originating from the left bronchus.



Figures 10A and B Axial views of the cardiac chambers obtained by MRI. Note panel A has *black-blood* (spin-echo) images while panel B has *bright-blood* (gradient-echo) images. Bright blood images also provide functional assessment

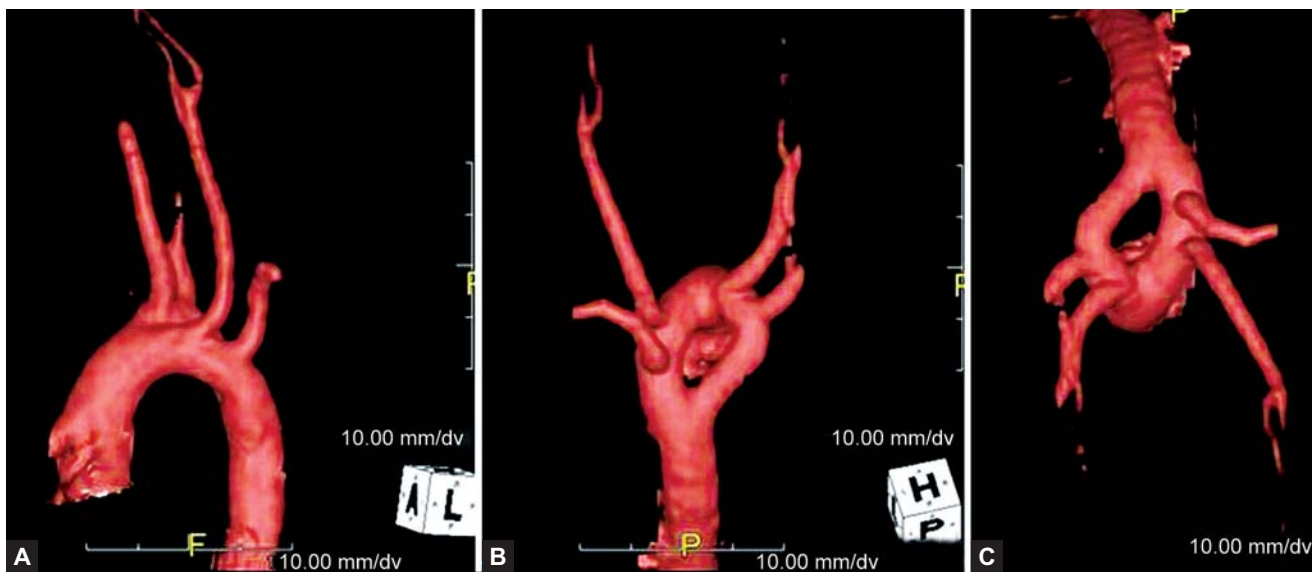
Cardiac CT is best suited for definition of anatomy of vascular structures in the chest and to appreciate their relationship to the surrounding nonvascular structures as in cases of vascular anomalies.

IN A NUTSHELL

1. Technologic advances in cardiac imaging have widened the choice for clinicians to choose the most suitable and least invasive modality based on the clinical condition of the child.

MORE ON THIS TOPIC

Allen HD, Moss AJ. Moss and Adam's Heart Disease in Infants, Children and Adolescents. 8th ed. Philadelphia: Wolter Kluwer/Lippincott Williams and Wilkins; 2013. pp. 207-46.



Figures 11A to C Double aortic arch—three-dimensional reconstruction from MRI images, providing detailed information regarding relative diameters of each aortic arch and their respective head and neck branches

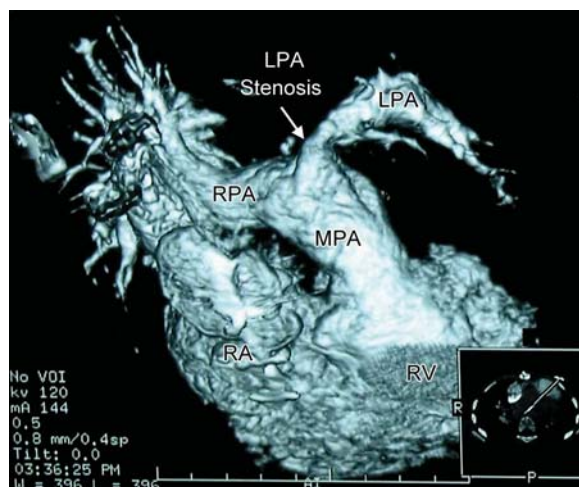
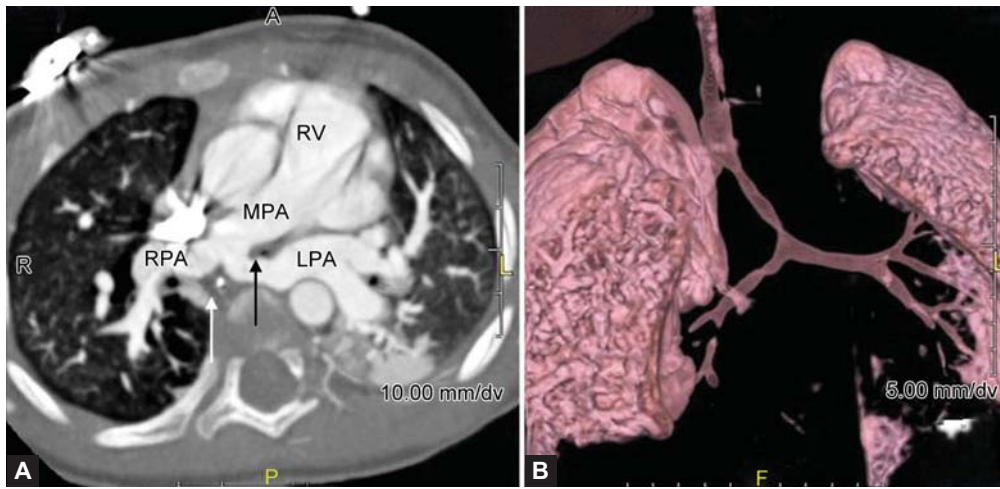


Figure 12 CT angiogram with three-dimensional reconstruction. Figure shows moderate, left pulmonary artery (LPA) stenosis in this 4-year-old girl who had tetralogy of Fallot repair at 10 months of age
 Abbreviations: RA, right atrium; RV, right ventricle; MPA, main pulmonary artery, LPA, left pulmonary artery; RPA, right pulmonary artery.



Figures 13A and B Cardiac CT scan in a 2-year-old child who presented with stridor, respiratory distress and failure to thrive. Left-side panel shows abnormal origin of LPA from RPA. Note the white arrow shows nasogastric tube in esophagus. Black arrow indicates the compressed lower trachea. Right-side panel shows lung window image reconstruction delineated the bronchial anatomy. Note the accessory, right bronchus. Due to recurrent right lower lobe pneumonia, this was treated by right lower lobe resection
Abbreviations: LPA, left pulmonary artery; RPA, right pulmonary artery.

Chapter 40.11

Cardiac Malpositions

P Syamasundar Rao

Cardiac malpositions are usually associated complex congenital heart defects (CHDs). This chapter presents an orderly, methodical and systematic approach to a patient with cardiac malposition. A brief discussion of heterotaxy syndromes will follow.

DEFINITIONS AND TERMINOLOGY

Normal position of the heart is in the left side of the chest (**Fig. 1**) and is expressed as *levocardia*. On the other hand, if the heart is in the right side of the chest (**Fig. 2**), it is described as *dextrocardia*.

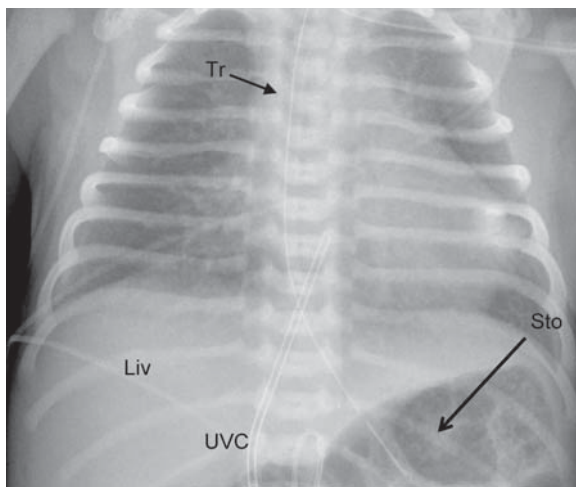


Figure 1 Normal position of the heart in the left side of the chest, also described as *levocardia*. The heart is shown on the left side of the chest. The liver (Liv) is on the right and the stomach (Sto) air bubble in left side of the abdomen indicating situs solitus. The trachea (Tr) is in the middle. Abbreviation: UVC, umbilical venous catheter.

Or, it may be in the middle of the chest (**Fig. 3**) when it is called *mesocardia*. Some cardiologists use the position of the apex of the heart to make this determination, but apicality of the heart cannot always be determined with certainty; more importantly, such determination is not necessary for the diagnostic approach to be described here. The heart may be pushed (**Figs 4 and 5**) or pulled to the right (**Fig. 6**); in such situation is called *dextroposition*. Other common terms are defined in **Box 1**.

BOX 1 Cardiac position terminology

- *Situs solitus*: Normal position of the viscera with the liver on the right side and the stomach on the left (**Figs 1 and 2**)
- *Situs inversus*: Left-to-right reversal of the viscera with the stomach on the right and liver on the left (**Figs 7 and 8**)
- *Situs inversus totalis*: Dextrocardia with situs inversus (**Figs 7 and 8**)
- *Isolated dextrocardia*: Dextrocardia with situs solitus (**Figs 2 and 9**)
- *Isolated levocardia*: Levocardia with situs inversus (**Fig. 10**).

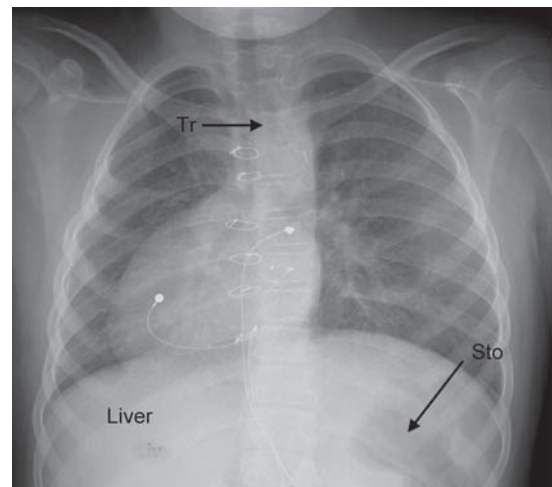
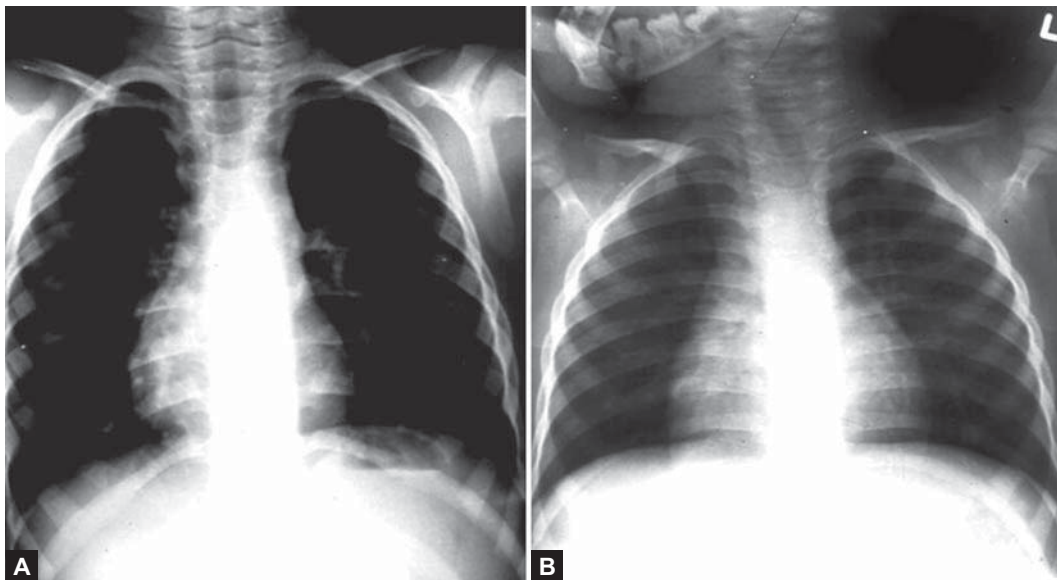


Figure 2 Chest X-rays of a child with dextrocardia; the heart in the right side of the chest. The liver (Liv) on the right and the stomach air bubble (Sto) in left side of the abdomen are indicating situs solitus. This is picture of isolated dextrocardia. The trachea (Tr) is in the middle. The sternal and pacemaker wires are related to prior surgery



Figures 3A and B Chest X-rays of two children with the heart in the middle of chest, described as *mesocardia*. The liver is seen across the abdomen without air in the stomach, making it difficult to ascertain atrial situs

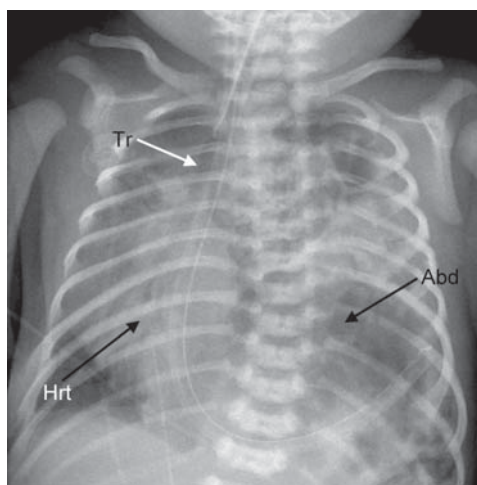


Figure 4 Chest X-ray of a baby with dextroposition of the heart (Hrt) secondary to diaphragmatic hernia on the left. The abdominal (Abd) contents including intestines are in the left chest and pushing the heart into the right chest. Note displacement of the trachea (Tr) to the right

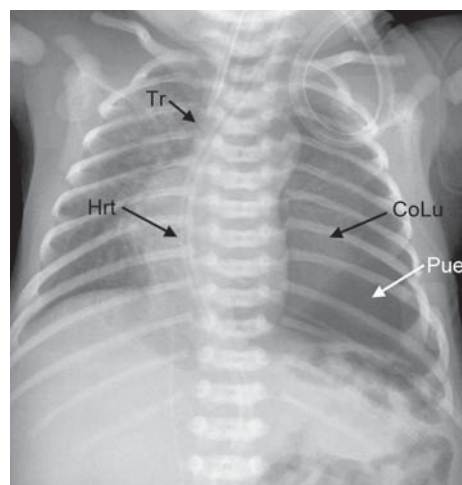


Figure 5 Chest X-ray of an infant with dextroposition of the heart (Hrt) due to pneumothorax (Pne) in the left chest pushing the heart into the right chest. Collapsed lung (CoLu) is shown. Note displacement of the trachea (Tr) to the right

EPIDEMIOLOGY

The heart is usually structurally normal in dextroposition. However, in dextrocardia, the prevalence of CHD is higher and the prevalence varies with the associated viscerotransposition. In situs inversus totalis, CHD is present in 3–10% of the babies while in isolated dextrocardia and isolated levocardia, CHD is present in almost 100% of the patients. This is in contradistinction to less than 1% CHD prevalence in normal population.

CARDIAC MALPOSITION: SEGMENTAL ANALYSIS

After dextroposition is eliminated, the cardiac malposition is evaluated by systematic segmental analysis. The approach is similar irrespective of levocardia, dextrocardia or mesocardia. Following exclusion of dextroposition and it is decided that the location of heart in the chest is intrinsic or primary (i.e., innate cardiac malposition), the following issues should be tackled:

1. What is the viscerotransposition?
2. *Ventricular relationship*: Are there two ventricles or one? If two, where are the ventricles located in relation to each other?
3. What is the status of atrioventricular (AV) connections?
4. How are the great arteries related to each other and with ventricles?
5. What is the conotruncal relationship?

1. Viscerotransposition

This may be situs solitus, situs inversus or situs ambiguus (symmetricus or indeterminatus). There are different ways by which the situs may be determined.

P waves in electrocardiogram (ECG) The cardiac impulse usually arises in the sinoatrial node which is located at the superior vena cava-right atrial junction and is transmitted inferiorly and to the left. The ensuing atrial depolarization produces P waves in the ECG. The P wave axis is 45° (Fig. 11) with positive P waves in leads I and AVF (Fig. 12). This is indicative of situs solitus with the right atrium on the right side. The atria are inverted in situs inversus and consequently, the P wave axis will be around 135° (Fig. 11) giving negative P wave in lead I and positive P wave in lead AVF (Fig. 13). If the P wave axis is -45° (Fig. 11), P waves in lead I are positive and

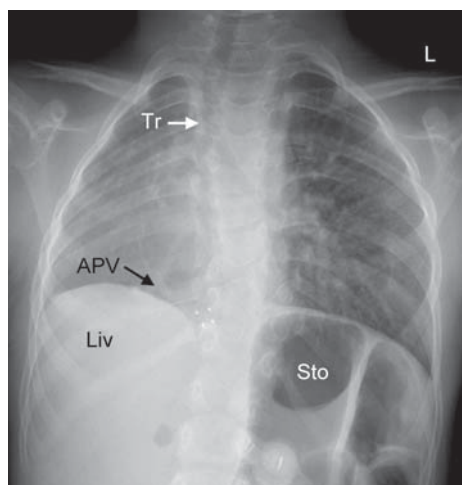


Figure 6 Chest X-ray of a child with dextroposition of the heart due to Scimitar syndrome. The heart is pulled to the right because of hypoplasia of the right lung. Anomalous pulmonary vein is shown (arrow, APV); the name of the syndrome is derived from this vessel because of its shape (Scimitar). Also note the displacement of the trachea (Tr) to the right

Abbreviations: Liv, liver; Sto, stomach.

P waves in lead AVF are negative (Fig. 14) and is called coronary sinus rhythm. Such P wave axis is not helpful in situs localization. Nevertheless, as reviewed latter, coronary sinus rhythm is often present in persistent left superior vena cava and infrahepatic interruption of inferior vena cava (IVC), which are frequently seen in asplenia/polysplenia syndromes.

Viscerotransposition concordance The universal tenet of viscerotransposition concordance suggests that right-sided liver and left-sided stomach (Figs 1, 2 and 9) are associated with morphologic right atrium on the right side and morphologic left atrium on the left side, i.e., situs solitus. On the converse, left-sided liver and right-sided stomach (Figs 7, 8 and 10) are indicative that morphologic right atrium is on the left side and morphologic left atrium on the right side, i.e., situs inversus. Similar sized hepatic lobes on both sides or a midline liver (Fig. 15), irrespective of the position of the stomach suggests

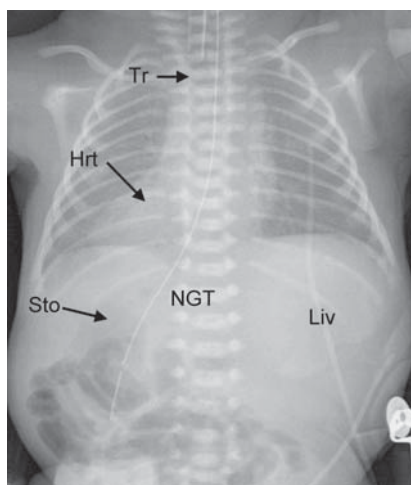


Figure 7 Chest X-ray of a neonate with dextrocardia. The heart (Hrt) is on the right side without displacement of trachea (Tr). The air in the stomach (Sto) is faintly seen on the right and the liver (Liv) on the left side of the abdomen; these findings suggest situs inversus. In addition, the position of the stomach on the right is confirmed by the position of the nasogastric tube (NGT). Since there is dextrocardia along with situs inversus, it is situs inversus totalis

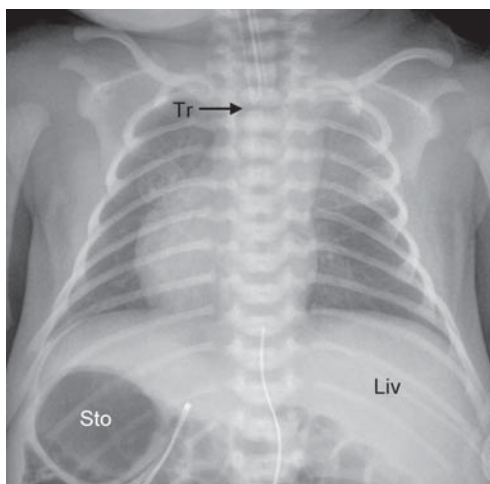


Figure 8 Chest X-ray of an infant with dextrocardia and situs inversus, i.e., situs inversus totalis. No displacement of trachea (Tr) is seen
Abbreviations: Hrt, heart; Liv, liver; Sto, stomach.

that situs ambiguous may be present and asplenia/polysplenia syndromes are likely. Visceroatrial concordance appears to be more consistent than P wave axis in ECG in appropriately identifying atrial situs.

Tracheobronchial tree pattern In normal children with situs solitus, the right bronchus is short and wide and descends steeply whereas the left bronchus is long and narrow and descends more horizontally (**Figs 16A and 17**). In individuals with situs inversus, the tracheobronchial tree pattern is reversed (**Figs 16B and 18**). This method appears to be more precise than the two above described methods. If both bronchi have morphologic appearance of right bronchus (**Fig. 19A**), asplenia syndrome should be considered and if morphologic appearance is that of left bronchus on both sides (**Fig. 19B**), polysplenia syndrome is likely. Exception to these rules can occur but rare.

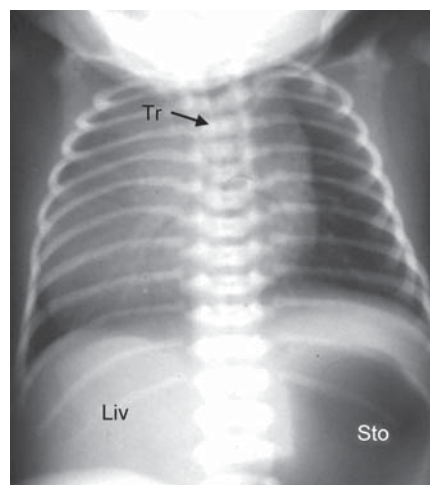


Figure 9 Chest X-ray of a neonate with isolated dextrocardia; i.e., dextrocardia with situs solitus with the liver (Liv) on the right and the stomach (Sto) on the left. No displacement of trachea (Tr) is seen

Vena cava-aorta relationship A constant relationship between the IVC and aorta (Ao) exists at the level of diaphragm; this may be visualized by short axis echocardiographic views (**Fig. 20A**). The vessels may be identified by their sizes (IVC larger than Ao), direction of flow (towards the heart for IVC and away from the heart for the Ao) and pulse wave characteristics (**Figs 20B and C**). In situs solitus (normal), the IVC is to the right of the spine and the Ao to the left of the spine, whereas in situs inversus, they are reversed. In dextro-isomerism (asplenia syndrome), the Ao and IVC are together on either side of the spine with the Ao anterior to the IVC. In levo-isomerism (polysplenia syndrome), the Ao is in the midline and the azygos is posterior to the aorta either on the right or on the left of the spine, depending upon whether there is azygos or hemiazygos continuation of the infrahepatic interruption of the IVC. Thus, the relative positions of the Ao and IVC are useful in the assessment of the atrial situs.

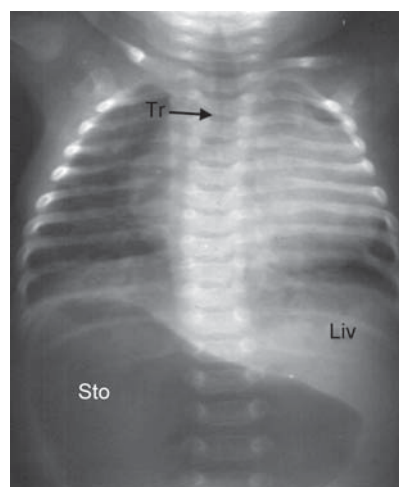


Figure 10 Chest X-ray of a neonate with isolated levocardia; i.e., levocardia with situs inversus with the stomach (Sto) on the right and the liver (Liv) on the left. Markedly dilated Sto is likely related to intestinal obstruction secondary to malrotation. No displacement of trachea (Tr) is seen

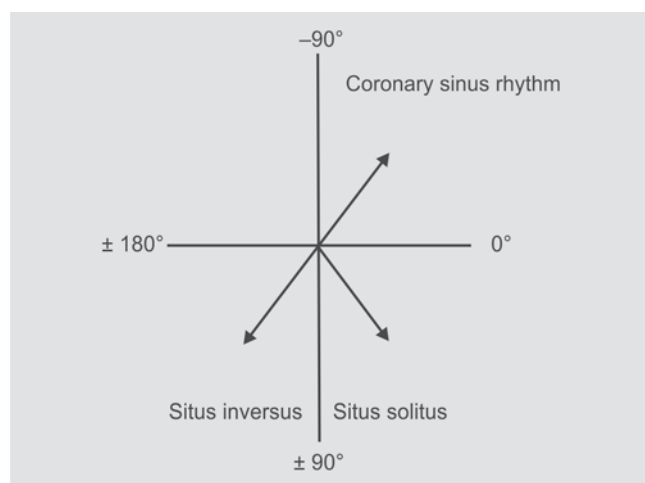


Figure 11 Utility of P wave axis (vector) in the frontal plane: P wave axis between 0° and $+90^\circ$ suggests situs solitus of the atria (normal), P wave axis between $+90^\circ$ and $\pm 180^\circ$ is indicative of situs inversus and P wave axis between 0° and -90° is likely to be coronary sinus rhythm; the last is not usually helpful in situs localization

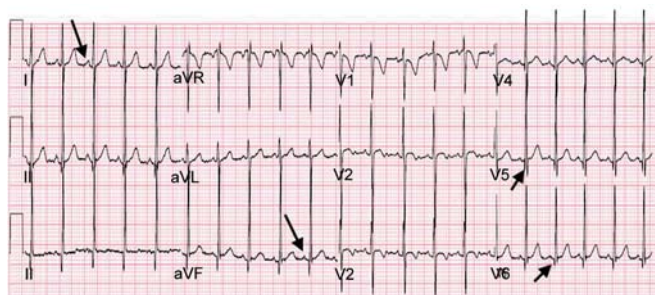


Figure 12 ECG demonstrating normal P wave vector of $+45^\circ$ with positive P waves (long arrows) in both leads I and aVF; this indicative of situs solitus. Also note Q waves in leads V5 and V6 (small arrows) and no Q waves in right chest leads; this is suggestive normal septal depolarization and, therefore, normal interventricular relationship

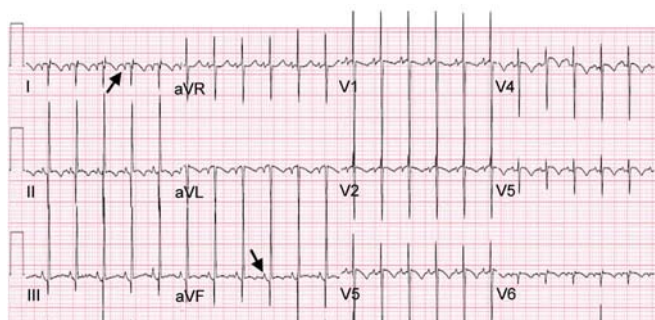


Figure 13 ECG demonstrating P wave vector of $+135^\circ$ with negative P waves in lead I and positive P wave aVF (thick arrows); this indicative of situs inversus. There are no Q waves in chest leads; this pattern is not helpful in ventricular localization

Venoatrial concordance During the embryonic period, the IVC is connected to the sinus venosus, which later becomes right atrium. Consequently, the IVC is on the side of the right atrium. Therefore, right-sided IVC is associated with situs solitus and left-sided IVC with situs inversus. The position of the IVC is easily seen by echocardiography and helps localize the right atrium. More invasive

methods such as nuclear angiography or catheter position during cardiac catheterization are also reliable indicators. However, in the presence of infrahepatic interruption of the IVC with either azygos or hemiazygos continuation, situs determination cannot be made because of absence of IVC.

Transesophageal echocardiography/Selective atrial angiography/Surgical inspection The right atrial appendage is broad, large and pyramidal whereas the left atrial appendage is narrow, small and tubular. If transesophageal echocardiography, selective atrial angiography or surgical inspection is performed for other reasons, the distinctive atrial appendage shapes are useful to assess atrial situs.

2. Ventricular Relationship

There may be either one (single) ventricle or two ventricles; such a differentiation can be made by noninvasive studies such as echocardiography (**Fig. 21**) or by angiography. If there are two ventricles, one needs to determine, if there is normal right-to-left relationship or the ventricles are inverted. This may be ascertained by the following methods:

Electrocardiogram Electrocardiogram patterns of QRS morphology with qRs to indicate left ventricle (LV) and Rs to indicate right ventricle (RV) are not reliable because right ventricular hypertrophy is seen in most patients with cardiac malposition. In addition, single ventricle is present in many of these patients. However, the initial QRS vector may be useful. In patients with normally related ventricles (the RV on the right and the LV on the left), initial septal depolarization produces Q waves in leads V5 and V6 without a Q wave in leads V1 and V2 (**Fig. 12**). In patients with inverted ventricles [the morphologic left ventricle (MLV) is on the right and the morphologic right ventricle (MRV) on the left], the AV conduction system is also inverted; this will result in Q waves in leads V1 and V2 and no Q waves in leads V5 and V6 (**Fig. 14**). Whereas initial QRS vector analysis had good theoretical basis, because of severe right ventricular hypertrophy (or single ventricle) and varying degrees of rotation of the heart that is seen in many of the cardiac malposition patients may make such analysis not completely accurate.

Echocardiography and angiocardiology The characteristic anatomic features of the ventricles, namely, architecture of the ventricles, AV to semilunar valve relationship and AV valve attachments are useful in identifying relative positions of the ventricles. The MRV is coarsely trabeculated with triangular shape whereas the MLV is smooth-walled with fine trabeculations and is foot-shaped. It should also be noted that AV valves go with the ventricles; the mitral valve is always an essential component of the LV while the tricuspid is an integral part of the RV. Also, the mitral and aortic valves are in fibrous continuity with each other suggesting MLV since the LV does not have conal muscle while crista supraventricularis separates the tricuspid and pulmonary valves from each other in the RV. Furthermore, the medial leaflet of the mitral valve is attached to the interventricular septum somewhat higher than the attachment of the tricuspid valve (**Fig. 22**). Another key principle is the loop rule; as per the loop rule, semilunar valve relationship are predictive of the ventricular looping which in turn localizes the ventricles: aortic valve to the right of the pulmonary valve indicates d-loop, i.e., the RV is on the right side and aortic valve to the left of the pulmonary valve suggests l-loop, i.e., RV is on the left. Coronary artery anatomy is also useful in that the left anterior descending coronary artery arises from the left coronary artery in d-loop while the left anterior descending coronary artery arises from the right coronary artery in l-loop. All the above portrayed features can be defined by deductive echocardiography and selective cine angiography.

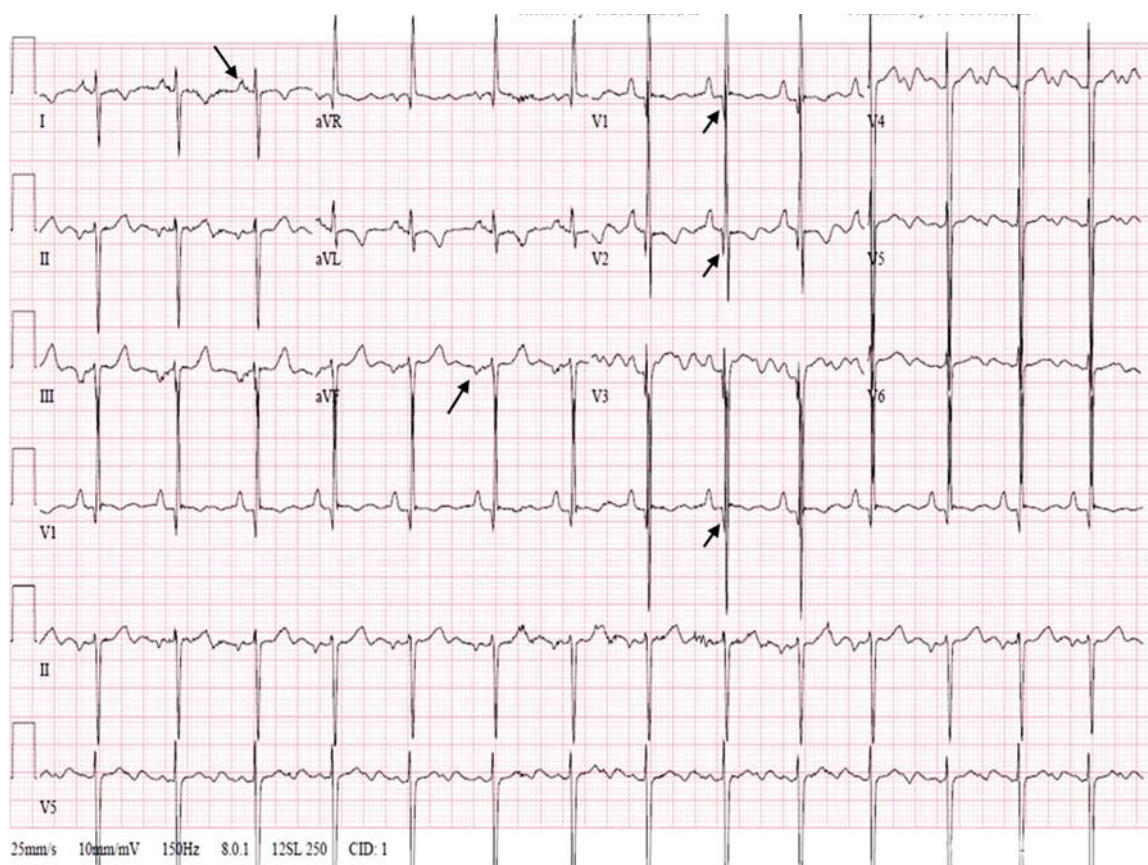
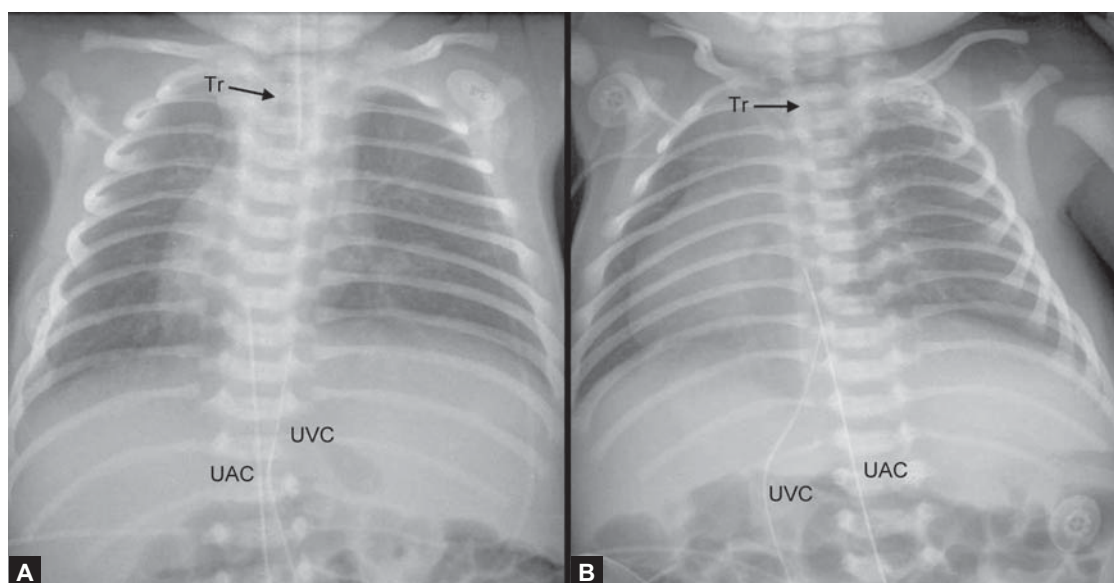
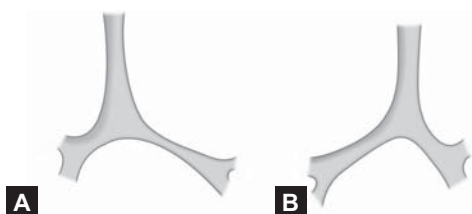


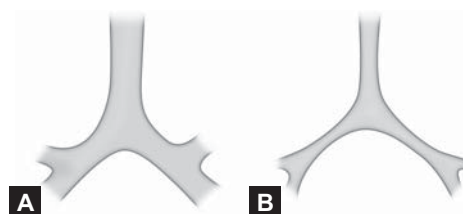
Figure 14 ECG demonstrating P wave vector of -45° with positive P waves in lead I and negative P wave AVF (long arrows); this is indicative of coronary sinus rhythm. Such a rhythm is unlikely to be helpful in situs localization. However, coronary sinus rhythm may be associated with persistent left superior vena cava and infrahepatic interruption of the inferior vena cava. Note Q waves in right chest leads (small arrows) and no Q waves in left chest leads; this is likely to indicate ventricular inversion. However, such pattern may be seen with severe right ventricular hypertrophy



Figures 15A and B Chest X-rays of two infants with dextrocardia with nearly equal sized hepatic lobes (and midline liver). The trachea (Tr) is in the middle. These infants were later shown to have asplenia syndrome. The positions of the umbilical venous catheters (UVC) and umbilical arterial catheters (UAC) are shown



Figures 16A and B Diagrammatic portrayal of bronchial anatomy. (A) *Situs solitus*: The right bronchus is short and wide and descends rather steeply while the left bronchus is long and narrow and descends more horizontally and (B) *Situs inversus*: The tracheobronchial tree pattern is reversed with the morphologic right bronchus on the left and the morphologic left bronchus on the right



Figures 19A and B Diagrammatic portrayal of bronchial anatomy in dextroisomerism and levoisomerism. (A) Asplenia syndrome. Both bronchi appear as morphologic right bronchi and (B) Polysplenia syndrome. Both bronchi appear as morphologic left bronchi

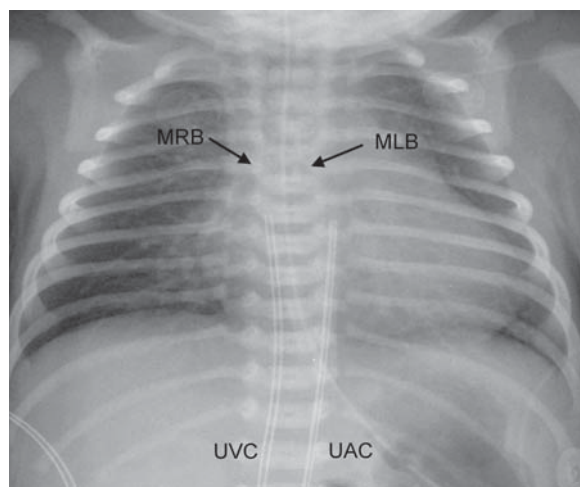


Figure 17 Chest X-ray of a baby with situs solitus; the morphologic right bronchus (MRB) is short and wide and descends rather steeply while the morphologic left bronchus (MLB) is long and narrow and descends more horizontally. The positions of the umbilical venous catheters (UVC) and umbilical arterial catheters (UAC) are marked

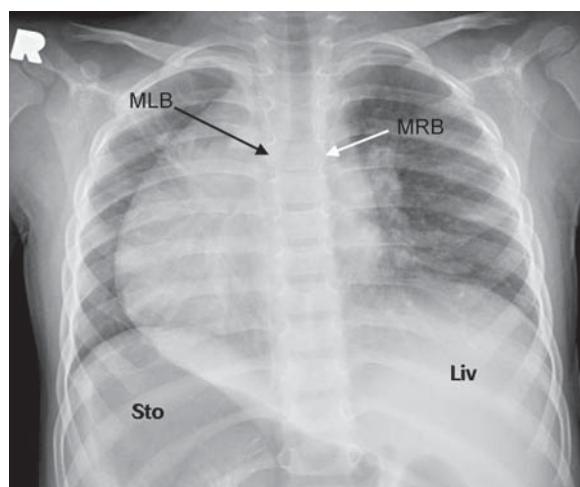


Figure 18 Chest X-ray of a child with dextrocardia with the morphologic right bronchus (MRB) on the left and the morphologic left bronchus (MLB) is on the right indicating situs inversus. The viscera are also inverted with the liver (Liv) on the left and the stomach (Sto) on the right

3. What is the Status of Atrioventricular Connections?

The connections between atria and ventricles may be concordant (right atrium connected to the RV and the left atrium to the LV), discordant (right atrium connected to the LV and the left atrium to the RV), only one common AV valve is present or one of AV valves may be atretic. Lastly overriding or straddling of the AV valve may be present or criss-cross relationship may be present. Again, these features may easily be identified by detailed echocardiograms, and if necessary by angiography may be performed.

4. How are the Great Arteries Related to Each Other and with Ventricles?

The great artery relationship may be normal in which case the aorta (aortic valve) is inferior, posterior and to the right of the pulmonary artery (pulmonary valve), may be inverted in which the aorta is to the left of the pulmonary artery, may have d-transposition with the aorta superior, anterior and to the right of the pulmonary artery, or may have l-transposition with the aorta superior, anterior and to the left of the pulmonary artery. The relationship may be portrayed as malposed, if it is abnormal, but cannot easily be placed into any of the above groups.

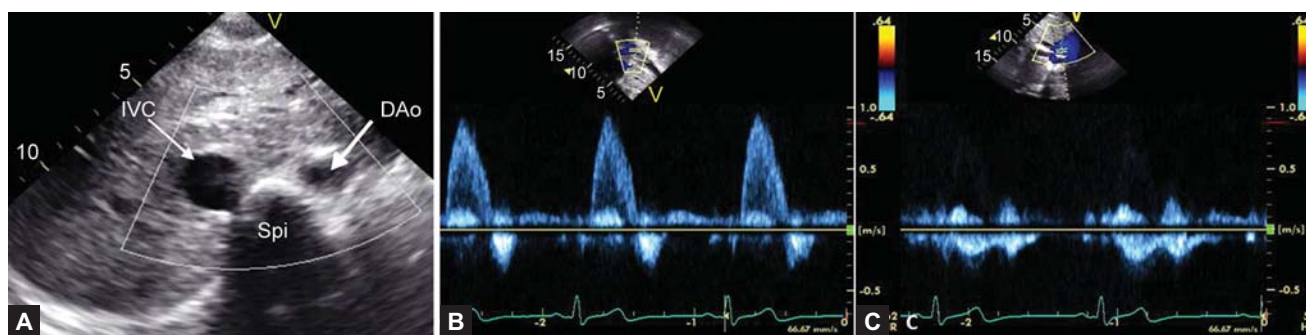
The connection of the great arteries with ventricles is also variable in that it may be concordant with the aorta arising from the LV and the pulmonary artery from the RV (normal), discordant with the pulmonary artery coming off of the LV and the aorta from the RV (d-TGA with d-loop or l-TGA with l-loop), double-outlet right ventricle (DORV) or double-outlet left ventricle with both great arteries arising from the RV or LV, respectively. There may be one vessel coming off the ventricles, truncus arteriosus or, there may be atresia of one of the semilunar valves or great vessels, i.e., pulmonary atresia or aortic atresia. Most of these relationships may be defined by echocardiography, although angiography or other imaging studies [CT scan or magnetic resonance imaging (MRI)] may be needed for confirmation.

5. What is the Conotruncal Relationship?

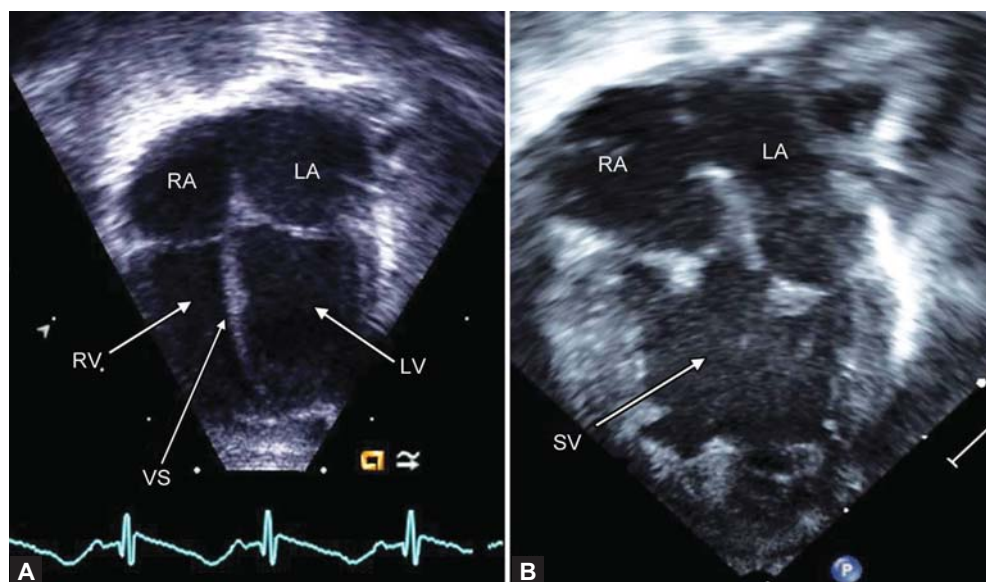
The conal tissue may be located in subpulmonary or subaortic regions, present bilaterally or absent. Subpulmonary conus is seen in normal hearts and subaortic conus is present in transposition. Bilateral conus is likely in DORV and conus is absent double-outlet left ventricle. The anteroposterior and superior-inferior relationship of semilunar valves indicates conal anatomy; the more conus beneath a semilunar valve, the higher and anterior is that valve.

Summary of Segmental Analysis

While cardiac position and atrial situs can be successfully appraised by routine physical examination, chest X-ray and



Figures 20A to C Selected video frame from a short axis echocardiographic view of a normal neonate demonstrating the inferior vena cava (IVC) on the right of the spine (Spi) and the aorta (Ao) on the left (A). The IVC is usually larger than aorta. Doppler flow patterns confirm higher velocity arterial flow pattern in the DAo (B) and low velocity venous flow in the IVC (C). This pattern suggests situs solitus



Figures 21A and B (A) Selected video frame from apical four-chamber echocardiographic view of a child with two ventricles. The right (RV) and left (LV) ventricles (thick arrows) are marked. The ventricular septum (VS) is shown (thin arrow) and (B) Selected video frame from apical four-chamber echocardiographic view a child with single ventricle (SV). No VS is seen
Abbreviations: LA, left atrium; RA, right atrium.

ECG, ventricular relationship, AV connections, great artery and conotruncal relationship need echocardiogram, angiocardiogram or other imaging studies for precise evaluation.

Segmental Assignment

After each cardiac segment is assessed, they may be suitably designated; atrial situs: S, solitus; I, inverted; A, ambiguous; ventricular situs: D, RV to the right or L; RV to the left; semilunar valves: S, solitus; I, inverted; D, d-transposition; L, l-transposition. For instance, normal hearts may be designated as (S,D,S), complete transposition as (S,D,D), corrected transposition as (S,L,L) and so on.

Associated Defects

After the sites of atria, ventricles and great arteries are established, the associated defects such as atrial and ventricular septal defects (VSDs), valvar stenosis or atresia and other abnormalities may be identified by usual methods such as physical examination, ECG, and echocardiography or angiocardiography or other imaging studies.

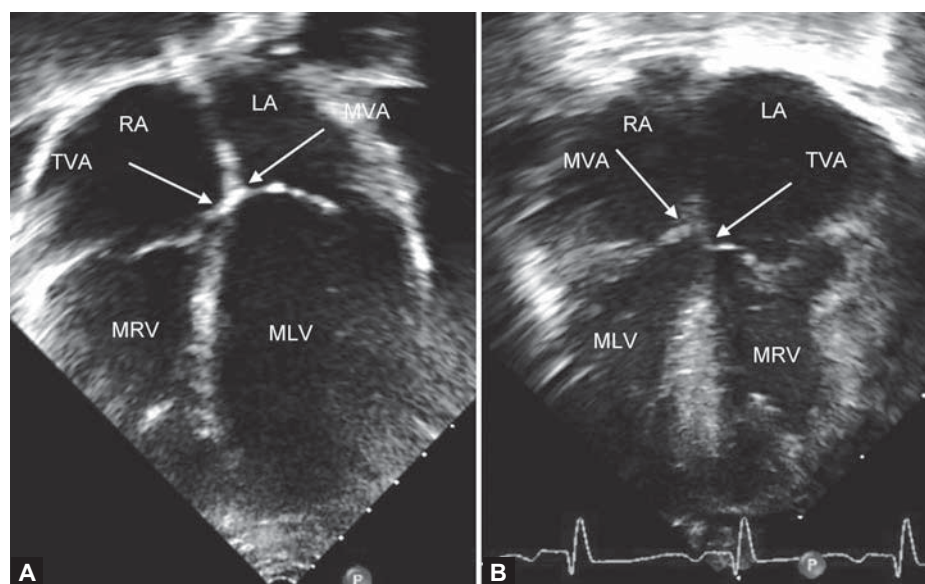
HETEROTAXY SYNDROMES

During embryonic development, left to right asymmetry is set-up in normal individuals with right-sided liver, left-sided stomach, tri-lobed right lung, bi-lobed left lung and normal right to left relationship of the atrial chambers and other structures. If embryological failure of development of such asymmetry occurs for any reason, heterotaxy syndromes such as asplenia, polysplenia and similar syndromes occur.

While papers on heterotaxy syndrome were published in 1826 by Martin and by Breschet, these entities are not commonly known until the publication of reports of case series by Ivemark and Putschar and Manion in mid-1900s. The prevalence of these syndromes is very low at 1 in 10,000 to 1 in 20,000 livebirths. Pathologic, clinical and diagnostic features and management of asplenia and polysplenia syndromes will be reviewed hereunder.

Extracardiac Anomalies

Asplenia syndrome The spleen is obviously absent in asplenia syndrome. As a result, the culling and pitting functions of the spleen are missing and consequently, Howell-Jolly and Heinz bodies as



Figures 22A and B (A) Selected video frame from apical four-chambered echocardiographic view of an infant with normal ventricular relationship; note higher level of attachment of the mitral valve (MVA) compared to the tricuspid valve attachment (TVA); and (B) Selected video frame from apical four-chamber echocardiographic views of an infant with ventricular inversion; note higher level of attachment of the mitral valve (MVA) on the right compared to the tricuspid valve attachment (TVA) on the left, indicating that the ventricles are inverted. This is a reversal of what is shown in A

Abbreviations: LA, left atrium; MLV, morphologic left ventricle; MRV, morphologic right ventricle; RA, right atrium.

well as abnormally shaped red cells (which are ordinarily removed by normally functioning spleen) are seen in the blood smear. Situs abnormality, generally described as situs ambiguous is seen in that there is bilateral right-sidedness (dextro-isomerism). The lungs are tri-lobed with eparterial bronchi on both sides. The hepatic lobes are symmetrical with the left lobe larger than the right and the liver is in the midline. The location of stomach variable; it may be on the left or right side. Malrotation of the midgut is seen with resultant intestinal obstruction and sometimes it may be the presenting symptom. The gallbladder is in the midline or may be absent.

Polysplenia syndrome In polysplenia syndrome, as the name implies, there are 2–9 equal-sized splenic masses, each of which is smaller in size than normal spleen, but total splenic tissue is comparable to normal splenic mass. However, functional asplenia is seen in some of the patients and Howell-Jolly and Heinz bodies may also be present in the blood smear. The situs is ambiguous in polysplenia syndrome, but with bilateral left-sidedness (levoisomerism). In general, there is a propensity for preservation of left-sided structures with hypoplasia or absence of right-sided structures. The lungs are bi-lobed with hyparterial bronchi on both sides. The liver is midline with somewhat symmetrical hepatic lobes. The stomach is situated either on the left or right side of the abdomen, malrotation of midgut may also be present which may either be nonrotation and less commonly reversed rotation. These abnormalities can result in intestinal obstruction, similar to that described in asplenia syndrome. The gallbladder is usually absent and biliary atresia may be seen.

Cardiac Defect

Asplenia syndrome Dextrocardia is frequent in asplenia syndrome patients. The incidence of cardiac abnormalities is very high although one earlier study cites only 63% prevalence of CHD. Both atrial chambers are morphologically right atria and common atrium is frequent. Atrial septal defects (ASDs) are typically seen with ostium primum type being more frequent; this may be a part of common AV canal. Common AV canal is present in the majority

patients. Single ventricle and ventricular inversion are common. Most patients with two ventricles have VSDs. Great arteries exhibit malposition which may manifest either as complete transposition (d-TGA), corrected transposition (l-TGA) or DORV. Atresia of the pulmonary valve or severe stenosis is present in almost all patients. Anomalies of the systemic veins, such as bilateral superior venae cavae are frequent in asplenia syndrome. Total anomalous pulmonary venous connection (TAPVC) is seen in two-thirds of the patients. However, partial anomalous pulmonary venous connection is uncommon.

Polysplenia syndrome Dextrocardia and levocardia are nearly equally present in polysplenia syndrome. Because of levoisomerism both atria are morphologically left atria. Common atrium is rare; this is in contradistinction to that seen in asplenia syndrome. ASD is present in 90% of patients; it is of ostium primum type in half of these subjects and ostium secundum in the remaining half. More often than not both ventricles are present and ventricular inversion is unusual. VSD is seen in 75% of patients while common AV canal is present only in 25% of patients. Complete transposition is unusual and DORV is uncommon. Pulmonary valvar atresia or severe stenosis is present only rarely; most patients do not have pulmonary outflow tract obstruction. Infrahepatic interruption of the IVC with azygos or hemiazygos continuation and bilateral superior vena cavae are commonly seen in polysplenia syndrome. Partial anomalous pulmonary venous connection is present in 50% of patients and TAPVC in one-third of patients; the pulmonary veins are connected directly to the venous atrium. Hypoplastic left heart syndrome and subaortic obstruction are rarely seen in polysplenia.

Clinical Features

Asplenia children present with severe cyanosis because of pulmonary oligemia secondary to complex CHD with severe PS or pulmonary atresia that they characteristically have. Signs of CHF are remarkably absent. Polysplenia babies, on the other hand, have mild or no cyanosis, often have increased pulmonary blood flow and may have signs of CHF.

When to Suspect Asplenia/Polysplenia Syndromes

The heterotaxy syndromes may be suspected, if there is inconsistency of situs by various methods discussed in the preceding section. Other features that increase the possibility are: (1) symmetric bronchial pattern (**Fig. 19**) with either dextro-isomerism (bilateral morphologic right bronchi) or levoisomerism (bilateral morphologic left bronchi); (2) divergence between cardiac position and viscerotaxial situs (isolated dextrocardia or isolated levocardia); (3) midline or symmetric liver on chest X-ray; (4) abnormal venous shadows on chest X-ray to indicate infrahepatic interruption of the IVC (or demonstrated by echo or angiographic studies) and (5) malrotation of the gut (nonrotation or reversed rotation).

Confirmatory Studies Useful in Splenic Syndromes

Howell-Jolly bodies and Heinz bodies As pointed out earlier, the culling and pitting functions are absent in asplenia and as a result, Howell-Jolly and Heinz bodies as well as abnormally shaped red cells which are normally removed by functioning spleen are seen in the peripheral blood smear. Indeed, some authorities have been suggested that in their presence a presumptive diagnosis of asplenia syndrome should be made. However, polysplenia patients may have functional asplenia resulting in appearance of Howell-Jolly and Heinz bodies in the blood smear. In addition, functional asplenia may be seen in babies with severe cyanotic CHD. Accordingly, the Howell-Jolly and Heinz bodies in the peripheral blood smear are not as useful in the diagnosis of asplenia in the neonate as once believed.

Barium gastrointestinal series When heterotaxy syndromes are suspected barium gastrointestinal studies should be undertaken in order to detect malrotation of the midgut. Malrotation of the gut in association with infrahepatic interruption of IVC is highly suggestive of polysplenia syndrome.

Abdominal ultrasound Abdominal ultrasound studies may be able to identify the liver and spleen and distinguish normal from asplenia and polysplenia. While this is possible in the hands of experienced ultrasonographers, rather similar ultrasound appearance of both liver and spleen makes this distinction confusing.

Radioisotopic scanning of the liver and spleen Radioisotopic scanning of the liver and spleen with ^{99m}Tc Technisium sulfur colloid is widely used to detect abnormalities of the liver and spleen. However, since such scanning tests the function of reticuloendothelial cells, which are present in both liver and spleen, it may be difficult to easily identify and separate these structures, particularly when they are abnormal. In addition, hypofunction of the splenic tissue in polysplenia syndrome may further confuse this issue. Use of radioactive material that specifically images liver or spleen (for example ^{99m}Tc Pipida) and superimposing them on ^{99m}Tc Technisium sulfur colloid scan may help to identify the splenic abnormalities.

Selective angiography Selective celiac-mesenteric artery and abdominal aortography may help to identify multiple rounded vascular densities of the splenic tissue.

DIAGNOSIS

Whenever cardiac malpositions and/or heterotaxy syndromes are suspected, segmental analysis, discussed earlier should be pursued and atrial, ventricular and great artery locations identified and segmental subsets assigned. Once the sites of atria, ventricles and great arteries are known, the associated defects such as ASDs, VSDs, valvar and vascular stenosis or atresia, etc. may be identified by cautious review of the history, systematic physical examination

and detailed analysis of ECG, chest X-ray and echocardiographic studies. If necessary, other noninvasive studies such as MRI and computed tomographic studies and invasive cardiac catheterization and selective cineangiography may be performed to authenticate the diagnoses.

MANAGEMENT

Palliation

Initial management of these babies is similar that used in other cyanotic CHD. The infant's temperature is monitored and neutral thermal environment maintained. If there is hypoxemia, oxygen is administered. In cyanotic CHD neonates, O_2 concentration should not be more than 40% because of fixed intracardiac right-to-left shunting higher levels of ambient O_2 do not increase O_2 saturation. Instead, the lungs are exposed to damaging levels of O_2 . When present, metabolic acidosis ($\text{pH} < 7.25$), is treated with sodium bicarbonate (usually 1–2 mEq/kg diluted half and half with 5% or 10% dextrose solution). If respiratory acidosis is present, suctioning, intubation and assisted ventilation is provided, as deemed appropriate. Because hypoglycemia may be a significant problem, the babies' serum glucose is watched. If hypoglycemia ($< 30 \text{ mg}/100 \text{ mL}$) is present, 15–20% dextrose solution is administered intravenously. Similarly, calcium concentration is monitored, and if hypocalcemia is found, it should be corrected.

After the baby is stabilized, treatment should address the physiologic abnormality produced by multiple defects that many of these heterotaxy babies are likely to have. In patients with pulmonary oligemia secondary to pulmonary atresia or severe pulmonary stenosis and large interventricular communication (or single ventricle), administration of PGE_1 (initial dose of 0.05–0.1 mcg/kg/min, slowly decreasing to 0.02 mcg/kg/min) is the first step. This is followed by modified Blalock-Taussig shunt. Neonates with markedly increased pulmonary flow and CHF should be treated with anti-congestive measures. Subsequently, surgical repair of the defect is performed (if the defect is amenable to total correction). If that is not possible, pulmonary artery banding may be performed first to decrease the pulmonary artery pressure and flow and to prevent pulmonary vascular obstructive disease. A plan for total correction later should be made. However, it should be understood that because of high pulmonary vascular resistance at birth and slow regression of the resistance in the presence of large interventricular communication, these babies usually do not go into CHF within the first few days to weeks of life. These babies may be carefully observed with intervention planned a few weeks later. Babies with obstructive type of TAPVC should undergo immediate surgical correction.

Additional Surgery

After initial palliation, methodical review of all the studies should be made to determine the feasibility of biventricular repair. If such is not possible, consideration for single ventricle palliation should be given with palliation early as detailed in the preceding section, bidirectional Glenn at about 6 months of life and Fontan conversion a year or 2 years later.

Noncardiac Issues

Because of lack of splenic function, these babies are at a higher risk for development of infection. During infancy, they should receive prophylactic doses of amoxicillin and switched later in childhood to penicillin. The risk of development of gastrointestinal obstruction is high. Consequently, prophylactic Ladd's procedure is performed routinely at many institutions to prevent gastrointestinal obstruction.

IN A NUTSHELL

1. Cardiac malpositions and heterotaxy syndromes have high prevalence of CHD; the prevalence is significantly higher than normal babies.
2. The incidence varies with the associated viscerotrial situs; isolated levocardia and isolated dextrocardia have the highest frequency.
3. The best approach to diagnosis is segmental analysis. In segmental analysis, the viscerotrial situs, ventricular location, status of atrioventricular connections, relationship of the great arteries and conotruncal relationship are determined with the help of ECG, chest X-ray and echocardiographic studies and when necessary other imaging studies, including angiography.
4. After the sites of atria, ventricles and great arteries are identified, the associated defects such as ASD, VSD, valvar and vascular stenosis or atresia may be determined by review of the history, physical examination and analysis of chest X-ray, ECG and echocardiographic studies.
5. At presentation, addressing the physiologic abnormality produced by the defect complex, whether it be augmenting pulmonary blood flow or restricting it, is the initial step. Other associated defects should also be addressed accordingly. Biventricular or univentricular repair depending upon the patients' anatomy should be planned.

MORE ON THIS TOPIC

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Chapter 40.12

Ventricular Septal Defects

IB Vijayalakshmi

Ventricular septal defect (VSD) is a developmental defect of the interventricular septum (IVS) wherein a communication exists between the two ventricular cavities. It can occur in isolation or as a part of more complex defects. Isolated VSDs can be repaired surgically with very low mortality rate. Recently, nonsurgical transcatheter device closure of VSDs is in vogue.

EPIDEMIOLOGY

Isolated VSDs are the second most common congenital heart disease (CHD) encountered after bicuspid aortic valves and occur in approximately 2 out of every 1,000 livebirths and constitute over 20–30% of all CHDs. The doubly committed subarterial or juxta-arterial defects are more common (30%) in Asian populations, whereas muscular and multiple defects are less common.

ETIOPATHOGENESIS

The etiology is multifactorial. Interaction between hereditary predisposition and environmental influences results in the defect. In the majority of patients with an isolated VSD (95%), the defect is not associated with a chromosomal abnormality and the cause is unknown. Studies have shown an interaction between *TBX5*, *GATA4*, and *NKX2.5*, suggesting that transcriptional activation may be responsible for septal defects. The VSDs may be associated with exposure to certain environmental factors during pregnancy especially within the first 8 weeks of gestation. Some of the environmental factors are maternal phenylketonuria, diabetes mellitus or exposure to febrile illness, especially rubella, influenza, or teratogens such as alcohol, cocaine, marijuana, ibuprofen, anticonvulsants (hydantoin, carbamazepine) or organic solvents.

Siblings of patients with VSD have three times the incidence of VSD as compared to general population. VSDs are found in 3.3% of the first-degree relatives and in nearly 3–10% of siblings of the index case. Maternal VSDs have a recurrence risk of 9–10%, whereas with paternal VSDs, the recurrence risk in the offspring is just 2–3%.

EMBRYOLOGY

The normal development of the IVS is a complex process and depends upon the endocardial cushions, conotruncal ridges, growth of tissues at the crest of IVS and the muscular septum. The

VSDs result from a deficiency of growth or a failure of alignment or fusion of the component parts of the IVS beyond the first 7 weeks of intrauterine life. The reason for this delayed or incomplete closure is still unknown.

CLASSIFICATION

The VSDs are classified depending on their locations on the IVS by Soto as seen from right ventricle (RV). They are divided into four types: (1) Perimembranous, (2) Muscular, (3) Outlet and (4) Inlet defects (**Table 1**). The diagrammatic representation of various locations of VSDs is given in **Figure 1**. The hemodynamic classification of VSDs is given in **Table 2**.

CLINICAL FEATURES

The signs and symptoms begin to develop when the fetal pulmonary hypertension starts declining sufficiently to permit left-to-right shunting. The clinical manifestation of isolated VSDs has a wide spectrum which varies depending upon the size of the defect and the magnitude of the shunt. It may range from being asymptomatic to severe heart failure. The infants with large VSDs present with symptoms due to congestive heart failure (CHF) in early infancy (2–6 weeks to 2–3 months). The signs and symptoms of VSDs are given in **Table 3**.

The systolic murmurs in outlet defects are heard in left second intercostal space (ICS) and may radiate upwards to the left into the suprasternal notch and into left side of neck. When the shunt is large ($Q_p/Q_s > 2:1$) a short mid-diastolic murmur is heard at the apex due to the increased flow across the mitral valve. When a small VSD is associated with severe aortic regurgitation (AR), one can hear a *to* and *fro* murmur. The *to* murmur is harsh long systolic crescendo and *fro* murmur is soft blowing early diastolic decrescendo murmur in the left second and third ICS. The patient will have the peripheral signs of AR. The jugular venous pulse is not raised in VSD.

NATURAL HISTORY

The natural history of a VSD varies widely, ranging from spontaneous closure to CHF to death in early infancy. It depends on type of the defect, its size, number and other associated anomalies. Spontaneous closure occurs in 25–40% of small VSDs by age of 2 years; 90% of VSDs that close do so by age of 10 years. The spontaneous closures are due to: (1) ingrowth of fibrous tissue with endocardial proliferation with septal aneurysm (may cause thromboembolism); (2) adherence of septal tricuspid leaflet resulting in tricuspid regurgitation; (3) prolapse of aortic cusp through the defect leading to AR and (4) vegetation of infective endocarditis which may lead to death.

Table 1 Types of ventricular septal defects with synonyms and anatomical features

Type of VSD	Synonyms	Anatomy	Conduction bundle
Perimembranous defects (80%)	Infracristal, subaortic, membranous, conoventricular	Membranous septum with extension into the adjacent inlet, outlet or muscular septum. They lie in the outflow tract of the LV immediately beneath the aortic valve	Posteroinferior margin of the defect
Muscular (5–20%)	Trabecular	Bounded by the muscular septum often multiple, it is often referred to as <i>Swiss-cheese</i> type of VSDs	Remote
Outlet (5–7%)	Supracristal, conal, infundibular, subpulmonary, doubly committed subarterial, doubly committed juxta-arterial	Subpulmonic communicating with the RV outflow tract above the supraventricular crest	Remote
Inlet (8%)	Canal-type, endocardial cushion-type, AV septum-type, inlet, juxtatriscuspid	Posteriorly and inferiorly to the membranous septum	Remote or the conduction system borders the defect superiorly

Abbreviations: VSD, ventricular septal defect; AV, atrioventricle; LV, left ventricle.

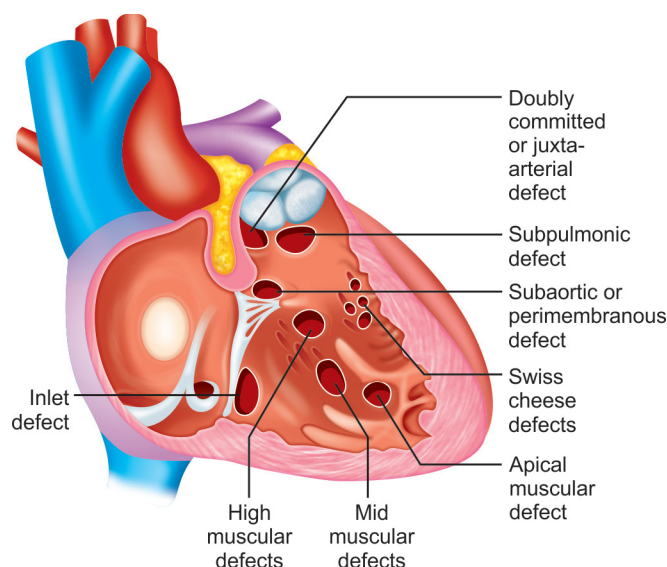


Figure 1 The anatomic position of various types of ventricular septal defects

Small defects may be closed by prolapse of aortic cusp leading to AR. The AR is due to Venturi's effect, seen more in subpulmonic VSDs (30%) than perimembranous VSDs (5–8%). It is more between the age of 5 years and 9 years. In nearly 5–10% of moderately to large VSDs, infundibular pulmonary stenosis (Gasul's effect) may develop. Large defects often develop left ventricular (LV) failure, pulmonary hypertension (Eisenmenger syndrome) and RV failure. Therefore, clinicians must not rush to tell parents that VSD in their child will close spontaneously. It must be told that every case must be followed up and evaluated clinically and by echocardiography (echo) to see whether the defect is becoming smaller.

DIAGNOSIS

Electrocardiogram (ECG) Inlet VSDs have left axis deviation (LAD). In multiple VSDs, 40% can have LAD. There can be broad notched left atrial P waves in L1 and L2 with broad P terminal force in V1. The tall R waves may be associated with tall, peaked T waves in L2, L3 and aVF. The leads V5-6 show prominent Q waves, tall R waves and tall, peaked T waves.

Transthoracic echocardiography (TTE) The TTE with color Doppler is widely used to diagnose VSD. The color Doppler can detect as small as 2 mm VSDs. The objectives of TTE assessment of a VSD are to define its site, size, hemodynamic effects, complications and associated lesions. This is accomplished by viewing the defect from multiple imaging planes (**Figs 2A to C**). The physiologic consequences can be assessed by the degree of LV

and left atrial dilatation as well as RV hypertrophy. The trans-VSD gradient of greater than 64 mm of Hg indicates a restrictive VSD with a normal pulmonary artery pressure. Also one needs to assess for potential complications such as bacterial endocarditis (**Figs 3A and B**) aortic cusp prolapse or AR (**Figs 4A and B**).

MANAGEMENT

The management of VSDs depends on the size, site, number of defects and magnitude of the shunt and also depends on the associated lesions and the complications. The small VSDs are usually asymptomatic and have an excellent long-term prognosis. They require just subacute bacterial endocarditis (SBE) prophylaxis. The small VSDs need periodic follow-up once in 6 months with monitoring of the symptoms, weight gain, and appearance of any new murmur of AR. Surgical closure of small VSDs is indicated (a) when there is associated moderate or severe AR and (b) if there has been a previous episode of endocarditis. The therapies available for management of VSDs are: (1) Medical, (2) Transcatheter, (3) Surgical and (4) Hybrid surgery.

Management of VSD in Newborn

Unless the defect is very small and uncomplicated, newborns with VSD need careful clinical and detailed echo reevaluations initially weekly and then bimonthly for first 8 weeks to detect early signs of volume overload. Detailed echo assessment has replaced catheterization. Prompt treatment of the lower respiratory infection (LRTI) and correction of anemia, must not be delayed. If the pulmonary artery systolic pressure is greater than half the systemic systolic pressure and CHF is difficult to manage medically with oral diuretics, then defect needs surgical closure without delay in the newborn period.

Management of VSD in Infants

If congestive failure is not severe, medical management is continued with oral diuretics only for a trial period of first 6 months. If the child is not gaining weight, is getting repeated LRTI and pulmonary artery systolic pressure is greater than half of the systemic systolic pressure, then the infant's defect is closed without further waiting. On the other hand, if the pulmonary artery pressure falls to less than half the systemic pressure, the infant is then managed medically till the end of their 2nd year of life. This decision must be supported by clinical improvement, weight gain, echo evidence of reduction in size and an increase in trans-VSD gradient.

Few children will remain symptomatic and continue to have cardiac enlargement beyond the 2nd year of life due to large left-to-right shunt despite the normal pulmonary arterial pressure. In such children surgical or device closure is recommended before the child enters the school. The criteria are: (i) QP:QS > 1.8:1, (ii) QP:QS > 1.5:1 in older children without severe pulmonary

Table 2 Hemodynamic classification of ventricular septal defects

	Small	Moderate	Large
Size (compared to aortic root)	< 1/3	1/3–2/3	> 2/3
Size orifical area (cm ² /m ²)	< 0.5	0.5–1.0	≥ 1.0
Peak systolic pressure gradient between LV and RV (mm Hg)	>64 High	≥ 20	< 20
Pulmonary/aortic systolic pressure ratio	<0.3	< 0.66	> 0.66
Shunt—Qp/Qs	< 1.5:1	> 1.5–2.2:1	> 2.2:1
LA/LV volume overload	Nil/minimal	+	++
PA pressure/PVR	Normal	↑	↑↑

Abbreviations: LV, left ventricle; RV, right ventricle; LA, left atrium; PA, pulmonary artery; PVR, pulmonary vascular resistance.

Table 3 Clinical features depending on size of ventricular septal defects

Size of VSD	Symptoms	Signs	Chest X-ray	ECG
<i>Small</i>	Asymptomatic, may be detected by murmur on a routine check-up	Precordial systolic thrill best felt in the left third and fourth ICS at the left LSB, grade 4/6, harsh holosystolic, crescendo-decrescendo murmur, best heard along the left LSB. In very small apical or muscular defects the murmur is soft, grade 2/6 or less, as the defect practically closes during systole	Normal	Normal
<i>Moderate</i>	Prominent pulsations over the precordium, mild tachypnea, fatigue or cough during feeding, lack of adequate growth with one or more episodes of LRTI. Effort intolerance and fatigue in older children	Precordial pulsations are visible due to the volume overload of LV. The apical impulse is LV type, hyperdynamic and is down and out indicating cardiomegaly. P2 is normal or mildly increased in intensity. Grade 3/6, low-pitched, systolic decrescendo murmur in LSB with mid-diastolic murmur in the mitral area	Moderate cardiomegaly, prominent PVM in both central and peripheral portions of the lung fields. The main PA segment is prominent. LA enlargement with wide carinal angle	Sinus rhythm, PR interval is normal or slightly prolonged. Normal QRS axis
<i>Large</i>	Infants present with symptoms due to CHF in early infancy (2–6 weeks to 2–3 months) tachypnea, lower chest retractions, feeding difficulties with suck rest suck cycle, excessive sweating of forehead, repeated LRTI and failure to thrive	Malnourished, tachypnea, chest retractions, precordial bulge with bilateral Harrison sulcus, prominent precordial pulsations, apical impulse is LV type, hyperdynamic and is down and out indicating cardiomegaly. P2 is palpable and loud with a narrow split. LV S3 can be present. Long crescendo decrescendo murmur in LSB	Cardiomegaly, pulmonary plethora, prominent main PA with RV enlargement. LV apex is displaced posteriorly due to RVH	Right axis deviation, biventricular hypertrophy is seen in the mid-precordial leads as large equidiphasic RS complex (> 50 mm), called as <i>Katz-Wachtel phenomenon</i> . With tall R wave in lead V1, deep Q waves, tall R and peaked, tall T waves V5–6
<i>Large VSD with high PVR</i>	Do not have much symptoms at rest, but have exertional dyspnea, cyanosis	Cyanosis and clubbing may be present. Left para sternal heave present. RV S3 present with RV type apical impulse. Very short soft decrescendo murmur or rarely no murmur is heard in balanced shunts. The ejection click may be heard due to PAH. P2 is quite loud, palpable with narrow split. No diastolic rumble at apex but a short early diastolic murmur of pulmonary regurgitation (Graham Steel's murmur) may be heard in left upper parasternal area	No cardiomegaly, RVH, aneurysmally dilated main PA, LPA and RPA, decreased PVM in the outer third of the lung fields (peripheral pruning)	Right axis deviation, P pulmonale, RVH
<i>Eisenmenger complex</i>	Easy fatigability chest pain, syncope and hemoptysis	Cyanosis, clubbing, loud palpable P2, parasternal heave, short soft systolic murmur in PA	Water jug appearance	Peaked P waves, right axis, tall monophasic R with small q and small s wave in V1

Abbreviations: CHF, congestive heart failure; CXR, chest X-ray; ECG, electrocardiogram; ICS, intercostal space; LRTI, lower respiratory tract infection; LA, left atrium; LPA, left pulmonary artery; LSB, left lower sternal border; LV, left ventricle; PA, pulmonary artery; PVM, pulmonary vascular markings; RPA, right pulmonary artery; RV, right ventricle; RVH, right ventricular hypertrophy.

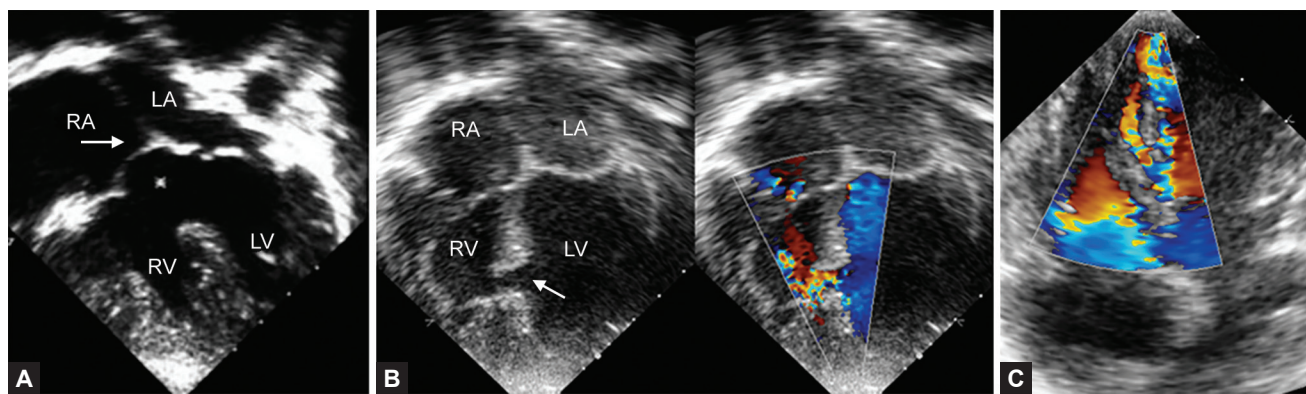
vascular resistance (PVR) and (iii) All patients older than 2 years, if pulmonary artery systolic pressure is greater than half the systemic arterial systolic pressure or mean pulmonary artery pressure is greater than 20 mm of Hg or PVR/systemic vascular resistance (SVR) ratio exceeds 0.2:1. The surgery is recommended, if calculated PVR is less than 11 units/m² or PVR/SVR ratio is less than 0.7:1 provided the QP:QS is still greater than 1.5:1. The patients with moderate VSDs need periodic medical follow-up. They need nutritional support for failure to thrive (FTT) and treatment of recurrent respiratory infections.

The indications (**Table 4**) and parameters for operability are presence of:

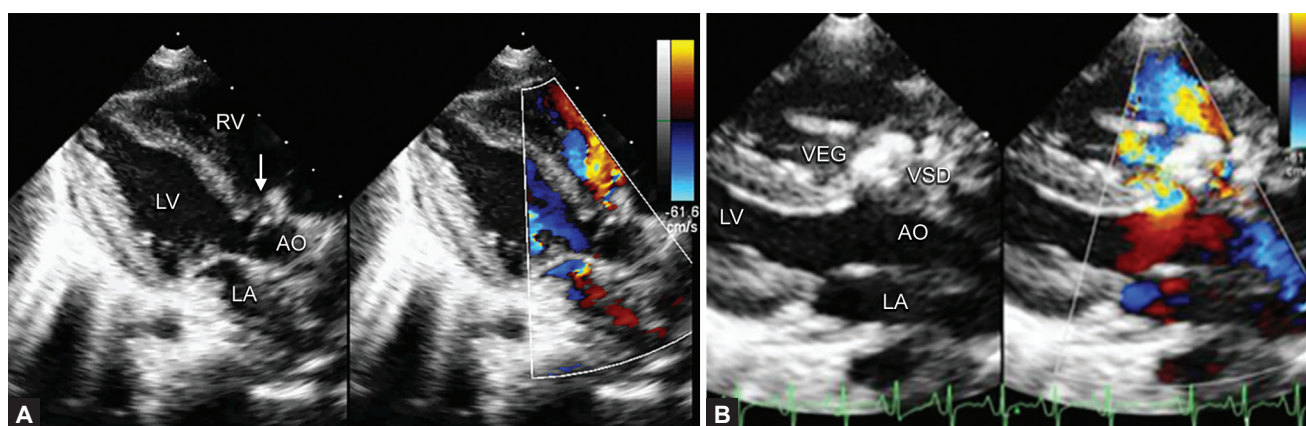
- Severe pulmonary arterial hypertension (PAH) in children less than 2 years
- Clinical symptoms of CHF, cardiomegaly, S3 and a mid-diastolic flow rumble at the apex

- Cardiomegaly with pulmonary plethora in Chest X-ray
- Presence of left ventricular hypertrophy (LVH) with volume overload in ECG
- Dilatation of left atrium (LA) and LV with sub-systemic PA pressure in echo
- Pulmonary vascular resistance index less than 6 Wood units and/or a ratio of pulmonary to SVR (Rp:Rs) less than 0.35 as catheterization data.

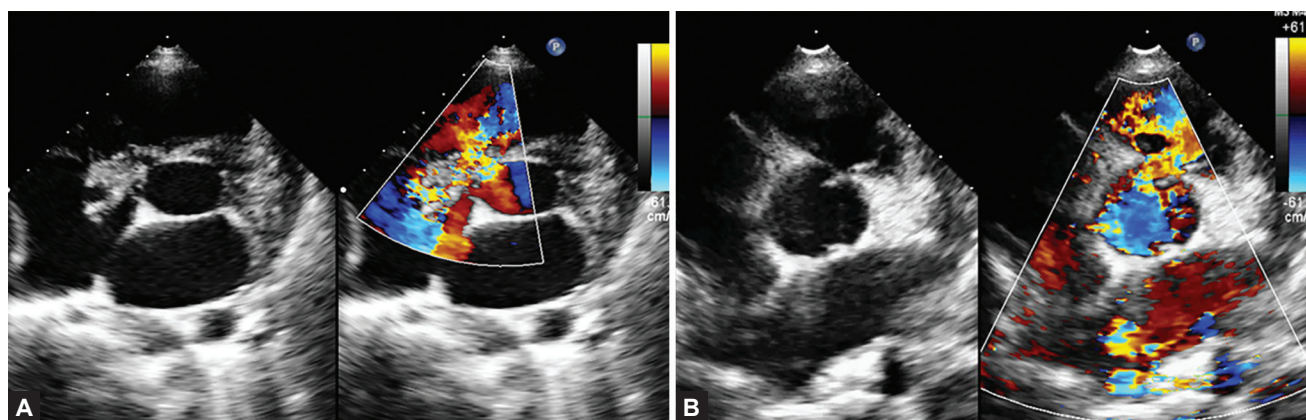
The closure of VSDs is based on the type of the VSD and ease of access. The current trend is to try to avoid a ventriculotomy as far as possible. Surgical closure is done in all large defects, inlet and outlet VSDs and in small VSD with past history of SBE. Neither the age nor weight is prohibitive in resorting to surgery. The nutritional support is vital and aimed to increase the caloric density of feeds. The LRTI has to be treated with antibiotics. The CHF is treated with a combination of drugs (**Table 5**).



Figures 2A to C (A) Inverted image of apical four-chamber view shows a large subaortic VSD; (B) Inverted image of apical four-chamber view with color Doppler shows mid-muscular ventricular septal defect (VSD) (arrow) with left-to-right shunt; and (C) Apical four-chamber view shows multiple Swiss cheese VSDs



Figures 3A and B Parasternal long-axis view with color Doppler shows small perimembranous ventricular septal defect (VSD) with septal aneurysm (arrow) and (B) Parasternal long-axis view with color Doppler shows large vegetation on right ventricle (RV) side closing the VSD



Figures 4A and B (A) Parasternal short-axis view with color Doppler shows subaortic ventricular septal defect (VSD) (in 9–10 o'clock position) with a vegetation and (B) Parasternal short-axis view with color Doppler shows subpulmonic VSD (1–2 o'clock position) just beneath the pulmonary valve with AR

Postoperative Follow-up

Children with preoperative PAH or elevated PVR should be followed up for 1–2 years after surgery. SBE prophylaxis is continued for at least 1 year. Holter monitoring is indicated in: (i) presence of symptoms suggestive of arrhythmia and (ii) in patients with postoperative right bundle branch block (RBBB)/left

anterior hemiblock. A redo surgery or device closure is needed, if residual shunt is significant.

Transcatheter Therapy

All mid-muscular VSDs, apical VSDs and selected cases of moderate sized perimembranous VSDs with at least 4 mm of aortic rim can

undergo nonsurgical transcatheter device closure (**Figs 5A to C**). The major advantages of device closure are absence of scar on the chest, less hospital stay and avoidance of cardiopulmonary bypass (CPB). Amplatzer septal occluder and Amplatzer duct occluder II (ADO II) are used to close VSDs. The ADO II is a very soft device with no polyester material and does not compress the conducting system. As it can be deployed from the aortic end, no arteriovenous looping is required. The arrhythmias are transient; complete heart block has been reported in 2–3% in perimembranous VSD device closure.

Hybrid Surgery

In small infants, when deploying large device is difficult, then hybrid surgery is done. The surgical and nonsurgical device closure is combined to close very large mid-muscular VSDs, especially

in infants with low body weight (< 5 kg). A mini sternotomy is done and then VSD device is deployed via purse-string suture on RV under echocardiographic and fluoroscopic guidance. The advantages are avoidance of CPB, less blood loss and speedy postoperative recovery.

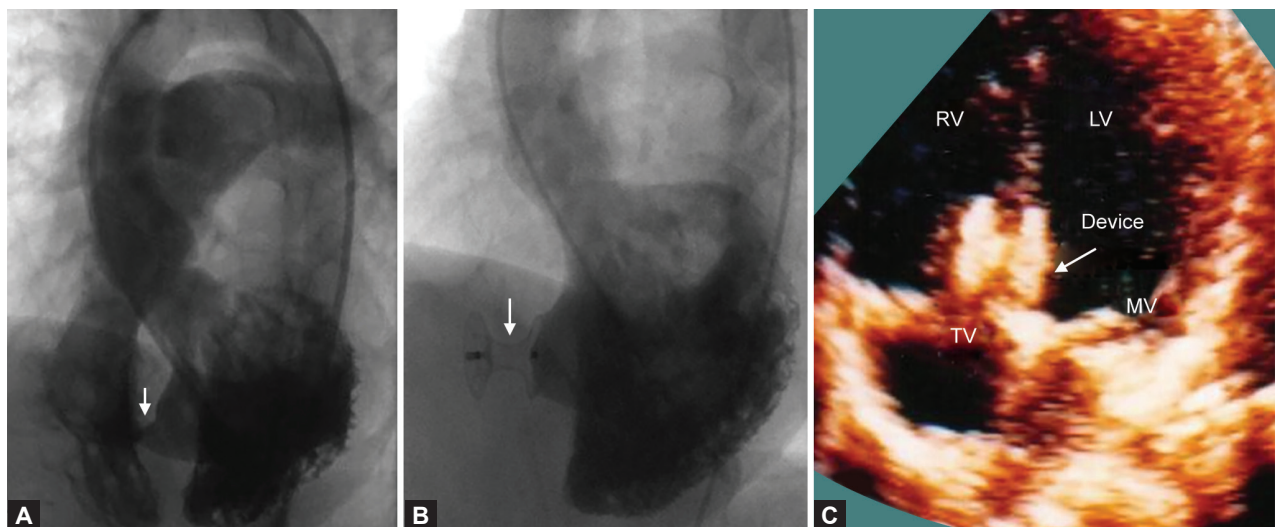
Table 4 The indications for surgery for VSD at different ages

Age	Indications
< 6 months	Uncontrolled congestive heart failure, failure to thrive
6–12 months	Pulmonary hypertension, symptomatic
2–5 years	Qp/Qs > 1.5:1, aortic regurgitation
> 5 years	Aortic regurgitation

Table 5 Drugs and doses for medical management of heart failure in children with moderate-to-large ventricular septal defect (VSD)

Drug	Dosage	Side effects
Diuretics (e.g., furosemide)	<i>Neonates, Premature:</i> Oral: 1–4 mg/kg/dose once or twice daily IM, IV: 1–2 mg/kg/dose administered every 12–24 hours <i>Infants and Children:</i> Oral: 1–6 mg/kg/day divided every 6–12 hours IM, IV: 0.25–2 mg/kg/dose every 6–12 hours	Long-term treatment—hypercalcemia and renal damage and electrolyte disturbances
Angiotensin-converting enzyme (ACE) inhibitors	Captopril—neonates and infants. Initial starting dose is 0.1 mg/kg/dose; gradually increased to 0.5–1 mg/kg/dose TID. Maximum dose is 2 mg/kg/dose Enalapril—older children Initial dose is 0.1 mg/kg/24 hour BID, gradually increasing to 0.5 mg/kg/24 hour BID	BP and renal parameters to be monitored
Digoxin	<i>Controversial:</i> 5–10 mcg/kg/day May be indicated, if diuresis and afterload reduction do not relieve symptoms adequately	

Abbreviations: IM, intramuscular, IV, intravenous.



Figures 5A to C (A) Left ventricular (LV) angiogram in LAO shows large mid-muscular VSD (arrow); (B) Check LV angiogram shows device in situ (arrow) with no residual shunt; and (C) Check echo shows device in situ with no residual shunt

IN A NUTSHELL

1. The ventricular septal defect is one of the most common CHDs.
2. A good clinical and echocardiographic assessment is important for timely management.
3. Surgery is the age old time-tested method of management for large defects and in inlet, outlet VSDs.
4. Device closure of VSDs, in selected patients, is an attractive alternative to traditional surgery.
5. In this modern era, no patient of VSD should be allowed to develop endocarditis, AR or Eisenmenger syndrome.

MORE ON THIS TOPIC

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Chapter 40.13

Atrial Septal Defects

K Sivakumar

Atrial septal defects (ASD) refer to open communication between right atrium (RA) and left atrium (LA) due to structural congenital defects in most instances. ASDs are classified according to their embryonic origin (**Fig. 1**).

- **Secundum ASD (75%)**—occur in central part of atrial septum in fossa ovalis
- **Primum ASD (20%)**—occur in the region of the endocardial cushion
- **Sinus venosus ASD (5%)**—in the sinus venosus septum
- **Coronary sinus ASD (very rare)**—in the region of ostium of coronary sinus
- **Vestibular ASD (extremely rare)**—in the region of the triangle of Koch above the septal tricuspid leaflet
- **Patent foramen ovale (PFO)**—normal fetal interatrial communication persisting beyond childhood.

INCIDENCE

Atrial septal defects account for 8–10% of congenital heart diseases (CHDs) in children. Male to female ratio is 1:2 in secundum defects and 1:1 in primum defects.

GENETIC FACTORS

Most defects are sporadic. The risk of CHD in infants born to a mother with ASD is 8–10%; mutations in regulatory genes or their target sarcomeric genes are reported in these children. Regulatory gene mutations in transcription factors NKX 2.5 (AD), TBX 5 in Holt–Oram syndrome (AD), familial ASD with AV nodal conduction delay (AD), TBX 20, *GATA 4* and *6* genes have been reported to be responsible for occurrence of ASD. Sarcomeric gene mutations (associated with cardiomyopathy) and missense mutation in alpha myosin heavy chain have also been identified in children with ASD. Syndromic associations with ASD include Down, Klinefelter, William, Kabuki, Goldenhar, Ellis-van Creveld syndromes and

Axenfeld-Rieger anomaly (glaucoma, dental anomalies, hernia and hypospadias). Maternal risk factors identified during pregnancy include diabetes, phenylketonuria, influenza, retinoids, nonsteroidal anti-inflammatory drugs (NSAIDs), antiepileptic drugs, thalidomide, smoking and alcohol.

ANATOMY

Secundum ASD It occurs as a single and rarely as multiple defects in the central part of fossa ovalis. It represents enlarged ostium secundum, caused by ectopic or excessive resorption of septum primum or deficient growth of septum secundum.

Primum ASD It occurs anteroinferior to fossa ovalis and guarded anteroinferiorly by the atrioventricular valves. They are invariably associated with cleft in the anterior mitral leaflet.

Sinus venosus defects These occur outside the margins of fossa ovalis, posterior to it. They are of two types. The most common is the superior vena cava (SVC) type defect, where the SVC orifice overrides the defect and is associated with anomalous drainage of right upper pulmonary vein to the right SVC. The rare right atrial type of sinus venosus defect is associated with anomalous drainage of right lower pulmonary vein into the RA and the inferior vena cava (IVC) orifice overrides the defect. This right atrial type of defect may be difficult to differentiate from a very large secundum ASD. Embryologically, the sinus venosus ASD occur due to unroofing of the right pulmonary veins causing their drainage into either SVC (in former) or RA (in later).

Coronary sinus ASD (called Raghbi's defect) is associated with complete or partial unroofing of the coronary sinus, resulting in shunting of left atrial blood through this unroofed coronary sinus into the RA through the enlarged ostium of the coronary sinus. This is often associated with persistent left SVC.

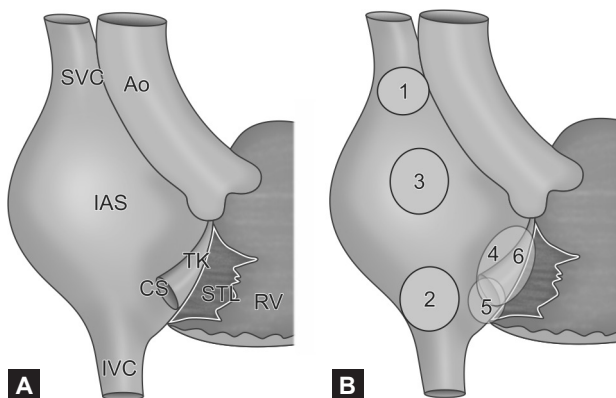
HEMODYNAMICS

Hemodynamics in Young Age

The persistence of high fetal pulmonary vascular resistance (FPVR) and fetal right ventricular hypertrophy limits the left to right shunt through ASD and hence children with ASD remain asymptomatic during this early period. With the gradual regression of FPVR and subsequent improvement in the capacitance of the elastic pulmonary artery and thinning of the right ventricle (RV) making it compliant and accommodative, the quantum of left to right shunt gradually increases resulting in increased pulmonary blood flow. The compliant RV tolerates volume overload well without rise of filling pressures. The capacitant pulmonary arterial bed accommodates high flows without increasing the pulmonary artery pressures. So, heart failure does not occur. Leftward shift of interventricular septum alters left ventricular geometry and causes mismatch between the relative sizes of the left ventricle (LV) and mitral valve leaflets. This leads to prolapse of the mitral leaflets and may lead to secondary mitral regurgitation. Repeated cuspal trauma leading to thickening and fibrosis of mitral leaflets increases the left to right shunt. Relentless increased pulmonary blood flow over many years eventually results in muscularization of the pulmonary arteriolar bed leading to late development of pulmonary arterial hypertension (PHT).

Hemodynamics in Later Childhood and Adulthood

The RV that efficiently manages the volume overload in early childhood, eventually fails to do so in later age and the right-sided filling pressures increases. This leads to congestive heart failure (CHF). Secondary tricuspid and pulmonary annular dilatation with regurgitation may further increase the right ventricular volumes.



Figures 1A and B (A) Cartoon illustration of interatrial septal surface of right with locations of superior vena cava (SVC), inferior vena cava (IVC), coronary sinus (CS), septal tricuspid leaflet (STL), ascending aorta (Ao) and triangle of Koch (TK); and (B) The locations of various types of ASD are indicated, (1) SVC type of sinus venosus defect, (2) IVC type of sinus venosus defect, (3) Secundum or fossa ovalis defect, (4) Primum ASD or partial atrioventricular canal defect, (5) Coronary sinus Raghbi's ASD and (6) Rarest vestibular ASD

Adult onset diseases such as systemic hypertension, atherosclerotic coronary ischemia and diabetic coronary microvascular disease cause left ventricular systolic and diastolic dysfunction and increase the left-sided filling pressures. This causes a secondary increase in the shunt in adult age. This additional increase of shunt tips the RV into CHF. In these older patients with elevated left ventricular end diastolic pressures, ASD closure will result in increase of left atrial and pulmonary venous pressures since they cannot pop-off their higher pressures into the right atria. This restrictive left ventricular physiology may worsen dyspnea after ASD closure. Enlarged right atrial size leads to atrial arrhythmias especially atrial fibrillation (AF). With advancing age, progressive vascular changes lead to PHT. The shunt reverses from right to left (Eisenmenger syndrome) usually after the fourth decade. They have a slow worsening of their symptoms and have a long natural history.

In a small minority of children with ASD, the progression of vascular changes in pulmonary circulation occurs disproportionately faster. In these patients, the pathology and progress of the PHT is akin to idiopathic PHT and the diagnosis of ASD becomes an incidental finding.

CLINICAL FEATURES

Symptoms

Most asymptomatic patients get detected on routine auscultation or incidental chest X-ray. Rarely, few infants may present with significant symptoms of growth failure and heart failure. The proposed reasons for this early symptomatology include rapid remodeling and thinning of the pulmonary vascular bed, failure of right ventricular myocardium to cope with volume overload, inappropriate increase of pulmonary artery pressures and underdiagnosed mitral valve abnormalities which augment the atrial shunt. These infants continue to grow slowly and remain symptomatic even after closure of the ASD.

Physical Findings

Jugular venous pressures are normal in early age, but with onset of heart failure or pulmonary hypertension, 'a' waves become prominent.

Precordium reveals prominent impulses in left parasternal border, subxiphoid area and pulsations in the left second intercostal space.

Heart sounds Tricuspid component of first heart sound is loud as the tricuspid valve leaflets are held far apart till end of diastole and there is wider excursion with onset of right ventricular systole. The classical hallmark of ASD is wide fixed splitting of the second heart sound. Increased right ventricular stroke volume caused by the shunted blood delays the right ventricular ejection and delays the pulmonary component of second sound. In the beginning of diastole, pulmonary valve closes at the point of the crossover of the falling right ventricular and pulmonary artery pressure curves. In patients with large ASD and low pulmonary artery impedance, the pulmonary valve continues to remain open even after the crossover of the pressure traces due to high capacitance of pulmonary arteries. This is called the long hangout interval. This widens the split, and is observed even in patients in pulmonary hypertension. Inspiratory increase of the systemic venous return augments right ventricular ejection and normally delays the pulmonary component of second sound. In patients with ASD, this inspiratory increase of systemic venous return will be compensated by a proportionate reduction in the left to right shunt and so the splitting remains fixed in different phases of respiration. The large pulmonary arteries have high capacitance to accept high pulmonary blood flows. During inspiration, there is no further increase of the pulmonary capacitance to allow higher flows. This also fixes the split. Even in

severe pulmonary hypertension, the associated right ventricular systolic dysfunction delays it and so the split remains wider.

Murmurs Flow systolic murmurs in pulmonary area (may very rarely lead to thrill in torrential shunts, or when associated with mild valvar pulmonary stenosis) and flow mid-diastolic murmurs in tricuspid area will be heard on auscultation. Rapid right ventricular diastolic filling leads to right ventricular third heart sound. PHT in later age leads to high frequency pulmonary early diastolic (Graham-Steell) murmur due to pulmonary regurgitation or left lower sternal pansystolic murmur due to tricuspid regurgitation.

Pulse Oximetry

Typically, oxygen saturations are normal. Hypoxia may be due to tricuspid valve hypoplasia or severe tricuspid regurgitation, right ventricular hypoplasia, pulmonary stenosis at any level or Eisenmenger syndrome. In some patients, it may be due to streaming of IVC blood in a right atrial form of sinus venosus defect or prominent Eustachian valve guarding the IVC orifice. It may also result from unroofed coronary sinus. Contrast echocardiogram with agitated saline will demonstrate occurrence of bubbles in the left-sided cardiac chambers and show right to left shunt.

DIAGNOSIS

Chest X-ray

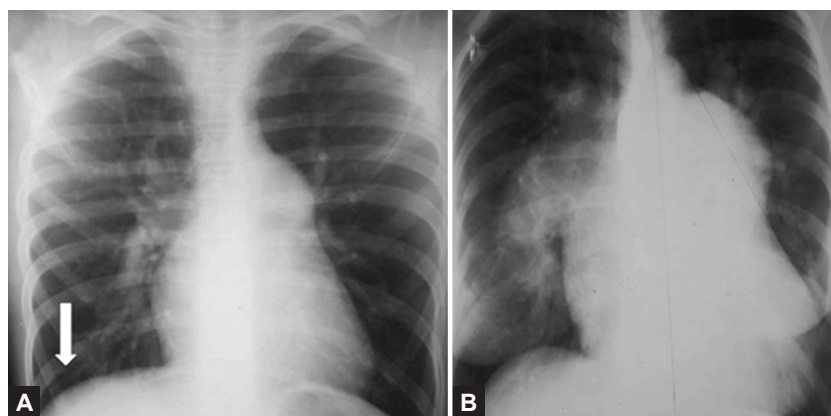
Findings include cardiomegaly, right atrial enlargement, dilated main pulmonary artery segment, inconspicuous aortic knuckle and plethoric lung fields where increased vascular markings extend to the peripheries (**Figs 2A and B**). The dilated RV lifts the cardiac apex from the left dome of the diaphragm at the left cardiophrenic angle. The retrosternal radiolucent space on a lateral view is obliterated. With onset of pulmonary vascular disease, peripheral pulmonary vascular markings get pruned but central pulmonary arteries get markedly dilated. The lower part of right SVC is dilated in SVC type defects.

Electrocardiogram

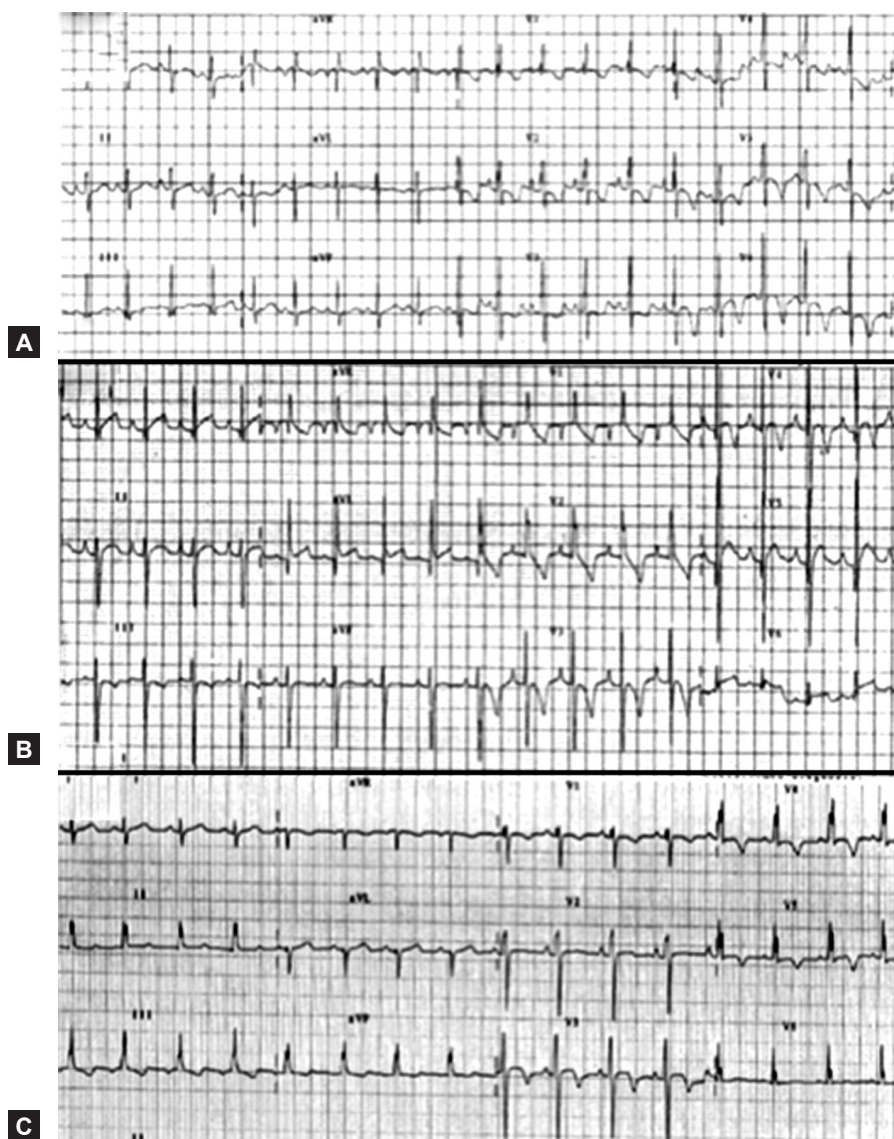
Right ventricular enlargement delays activation of the right ventricular outflow tract causing rsR' pattern in V1 (**Figs 3A to C**). In older patients, right atrial enlargement and right axis deviation of QRS axis occurs. Slurring of QRS waves in inferior leads called *crochetage sign* is seen very often. P axis is deviated leftwards in SVC type of sinus venosus defects. Primum ASDs show leftward QRS axis with counterclockwise loop, shown as deep *q* waves in I and aVL. 5% of secundum and sinus venosus defects may also have left axis deviation. Older patients may show sinus nodal disease, junctional escape rhythm, atrial ectopics, atrial arrhythmias including fibrillation. Onset of pulmonary hypertension leads to further right axis deviation of QRS axis, occurrence of *q* waves in V1 and increase of height of R' in V1. Certain familial ASD shows first or second degree AV nodal block. Respiratory sinus arrhythmia is almost never seen.

Echocardiogram

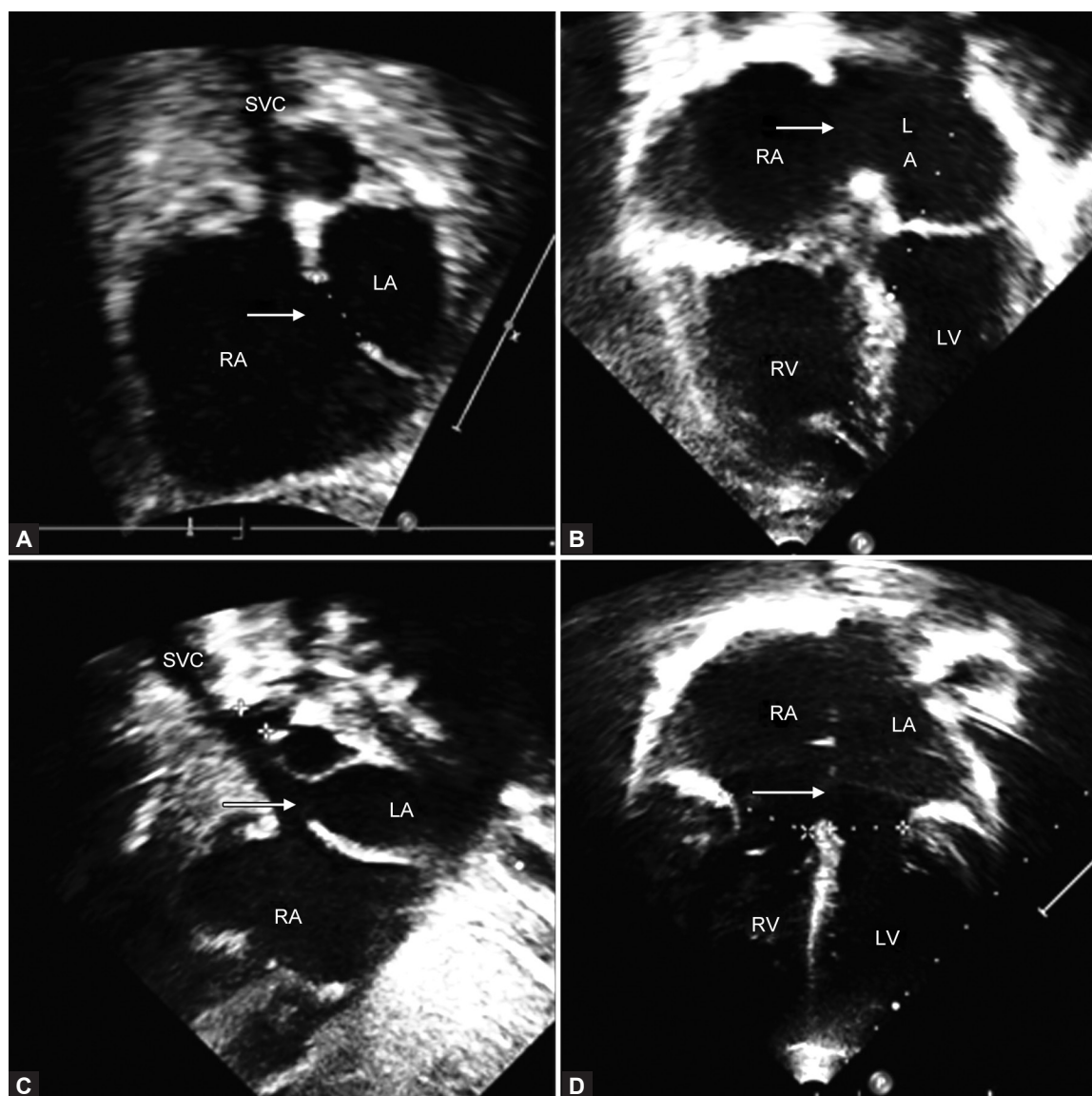
Location of ASD in the atrial septum differentiates the different forms of ASD (**Figs 4A to D**). Important common associations include anomalous pulmonary venous drainage (seen in 10%), mitral valve regurgitation (10%) and valvar pulmonary stenosis (10%). Doppler interrogation confirms direction of left to right color flow across the ASD, gives assessment of severity of pulmonary hypertension by tricuspid regurgitation jet, detects mitral regurgitation and pulmonary stenosis. Echocardiography also assesses the margins of the defect and identifies the defects amenable for device closure in the present era of nonsurgical interventions for most secundum defects.



Figures 2A and B Chest X-ray in ASD. (A) In large ASD with increased pulmonary blood flows, there is cardiomegaly, prominent main pulmonary artery segment, dilated right and left pulmonary artery shadows in both hilum. The pulmonary vessels can be tracked to the peripheral one-third of the lung fields as shown by the arrow and (B) Once pulmonary vascular occlusive disease occurs (Eisenmenger), the peripheries of the lungs get pruned of the blood vessels, the main pulmonary artery and hilar right and left pulmonary artery get aneurysmally dilated. The cardiomegaly increases further due to dilatation of right-sided chambers secondary to tricuspid and pulmonary regurgitation



Figures 3A to C ECG in ASD. (A) In secundum ASD, frontal QRS axis is deviated minimally to the right and there is rsr' pattern in lead V1; (B) Primum ASD characteristically demonstrates left axis deviation and counterclockwise looping shown as deep q waves in leads I and aVL and (C) SVC type of sinus venosus ASD may demonstrate leftward deviation of P axis from 0° to -30°



Figures 4A to D Echocardiogram in different types of ASD. (A) *Subxiphoid view*: Large secundum ASD in mid-portion of fossa ovalis shown in arrow; (B) *Apical view* demonstrates dilated right atrium (RA) and right ventricle (RV) in comparison to (C) Left atrium (LA) and left ventricle (LV). In contrast to secundum ASD (A), a sinus venosus ASD of SVC type occupies the posterosuperior part of septum on subxiphoid view and there is override of the superior vena caval orifice (SVC) into the right atrium and (D) Ostium primum ASD shown in an apical view, occupies the anteroinferior part of the septum and bounded by the atrioventricular valves

Cardiac Catheterization

Oximetry run from samples drawn from vena cava to pulmonary artery shows 7–10% step up in oxygen saturations at the level of RA. Other causes of step up in RA include Gerbode ventricular septal defect (VSD), VSD with tricuspid regurgitation, coronary fistula into RA, partial anomalous pulmonary venous drainage to RA and ruptured aortic sinus into RA. The shunt ratio (Q_p/Q_s) calculated with oximetry more than 1.5:1 indicates significant shunt and need for treatment. In patients with severe pulmonary hypertension, vascular resistances are calculated by pulmonary artery pressure measurements. If the pulmonary vascular resistance index is more than 8 Wood units, even after oxygen or other pulmonary vasodilators such as nitric oxide, patients are considered inoperable.

NATURAL HISTORY OF UNTREATED ASD

Most defects below 5 mm in neonates and infants close spontaneously, but defects larger than 8 mm seldom close. Apart

from 5% of young infants who present with severe heart failure, most children are asymptomatic. 25% of patients with ASD die by 30 years, 50% by 37 years, 75% by 50 years and 90% by 60 years. 14% of young adults develop progressive pulmonary hypertension and 6% develop Eisenmenger syndrome. 50% of patients aged 40 years have paroxysmal or permanent AF. Most adults develop heart failure.

TREATMENT

Medical Management

Asymptomatic children need no medications. The small subset of infants who present with severe heart failure and right ventricular dysfunction may require diuretics and digitalis. Patients with Eisenmenger syndrome may get symptom relief with pulmonary vasodilators namely sildenafil or bosentan. Amiodarone is given for medical cardioversion of AF and to prevent recurrences; digoxin controls ventricular rates in AF.

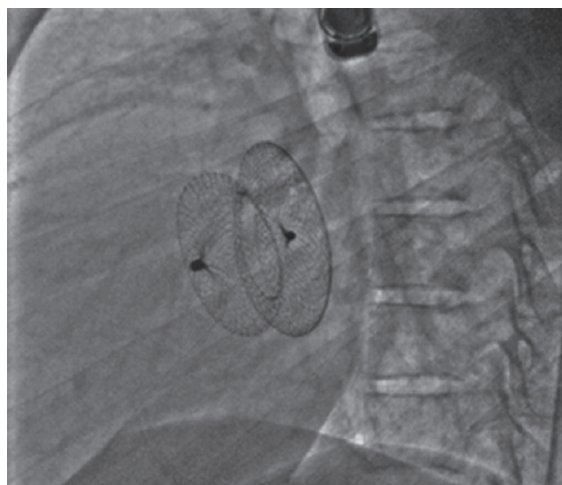


Figure 5 Lateral view chest X-ray after nonsurgical device closure of ASD with nitinol wiremesh occluder device demonstrating the two discs, the posterior left atrial disc is closer to spine

Surgical Correction

Open heart surgical correction of primum defects and sinus venosus defects are done at an appropriate age between 1 year and 5 years. Primum ASD with severe mitral regurgitation from cleft of anterior mitral leaflet may benefit from early surgery. Surgery of sinus venosus defect is often deferred till 4–5 years since surgical baffling of the right upper pulmonary veins to the LA in early ages may compromise the lumen of SVC RA junction. Most patients with secundum ASD are amenable for nonsurgical transcatheter management in current era, except very large defects with deficient margins. Instead of full sternotomy for surgical access, cosmetic approaches in recent times include ministernotomy (small midline incision), right anterolateral thoracotomy (inframammary incision in postmenarchal girls), right posterolateral thoracotomy (below the scapular line), minimally invasive cardiac surgery (using femorofemoral cardiopulmonary bypass and small chest incisions) and robotic surgery. These innovations limit the size of the surgical incisions markedly.

Nonsurgical Interventions

Currently, most secundum defects with adequate margins on echocardiogram are closed in cardiac catheterization laboratory with nitinol (nickel-titanium alloy) wire mesh occluder devices through femoral venous route under echocardiographic and fluoroscopic guidance (**Fig. 5**). This avoids cardiopulmonary bypass related complications, surgical scars, blood transfusions and mechanical ventilation. The hospital stay is short and recovery is early.

After the device closure, antiplatelet dose of aspirin is given for 6–12 months till complete endothelialization of the device. Complications such as device embolization, thrombus formation,

cardiac perforations and infection are extremely rare. In patients with severe pulmonary hypertension or restrictive left ventricular physiology, fenestrated devices allow a small flow through the atrial septum instead of a complete closure.

PATENT FORAMEN OVALE

While 25–33% of normal adults have been shown to have a probe patency of foramen ovale, a small right to left shunt with paradoxical embolism across PFO may lead to few cryptogenic strokes or transient ischemic attacks. PFO is also implicated in migraine with aura, decompression sickness, diver's illness and platypnea-orthodeoxia syndromes. In these patients, a right to left shunt is documented by agitated saline injection contrast echocardiography or transcranial Doppler study. Device closure of PFO is carried out in catheterization laboratory from femoral venous access.

IN A NUTSHELL

1. Most atrial septal defects are secundum ASD (75%) and occur in central part of atrial septum in fossa ovalis; 20% are primum ASD (20%) and occur in the region of the endocardial cushion.
2. The classical hallmark of ASD is wide fixed splitting of the second heart sound. CHF occurs only in later childhood. The RV that efficiently manages the volume overload in early childhood, eventually fails to do so in later age and the right-sided filling pressures increases.
3. Enlarged right atrial size leads to atrial arrhythmias especially AF. With advancing age, progressive vascular changes lead to pulmonary hypertension. The shunt reverses from right to left (Eisenmenger syndrome) usually after the fourth decade.
4. Most children are asymptomatic. 25% of patients with ASD die by 30 years, 50% by 37 years, 75% by 50 years and 90% by 60 years. Half of patients aged 40 years have paroxysmal or permanent atrial fibrillation. Most adults develop heart failure.
5. Open heart surgical correction of primum defects and sinus venosus defects are done at an appropriate age between 1 year and 5 years. Most patients with secundum ASD are amenable for nonsurgical transcatheter management in current era, except very large defects with deficient margins.

MORE ON THIS TOPIC

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Chapter 40.14

Atrioventricular Septal Defects

Snehal Kulkarni, Tanuja Karande

Atrioventricular septal defects (AVSD) are abnormalities of the atrioventricular septum and of the atrioventricular valves. They can also be identified as the atrioventricular canal defects and endocardial cushion defects.

As these children present with severe heart failure in early infancy, the possibility of AVSD should be kept in mind while evaluating a symptomatic infant with congestive heart failure. After confirming the diagnosis with echocardiography, these children need to be screened for possible chromosomal anomalies such as trisomy 21. They need aggressive medical management for control of heart failure. Complete recovery is possible with timely diagnosis and surgical repair.

INCIDENCE

Incidence of AVSD varies from 1.4% to 10.8% (4–5%) of all congenital heart defects. This constitutes 0.19 per 1,000 livebirths.

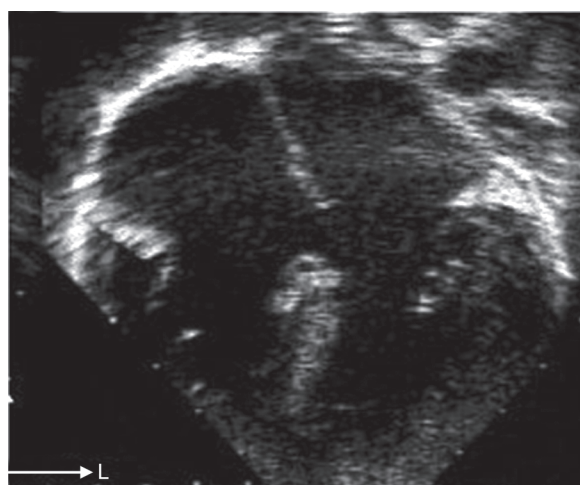
ASSOCIATIONS

Complete AVSD is the most common association with Down syndrome seen in approximately 40–50% of children. They are also more likely to have associated tetralogy of Fallot. Complete AVSDs also occur in patients with heterotaxy syndromes (more common with asplenia than with polysplenia). Common atrium has been associated with Ellis-van Creveld syndrome.

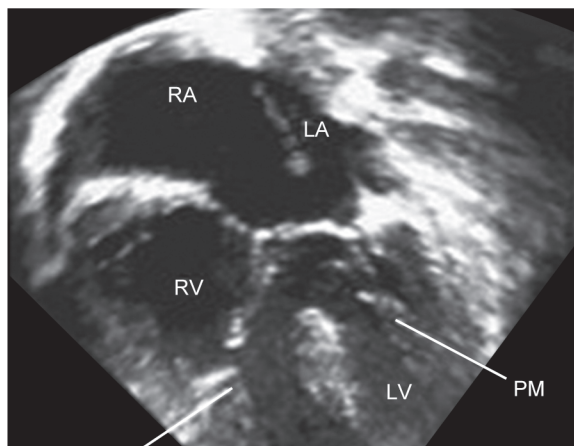
CLASSIFICATION (FIG. 1)

Atrioventricular septal defects either can be partial or complete depending upon their morphological characteristics. Primum atrial septal defect (ASD) is always a part of AVSD and there are two separate mitral and tricuspid valve annuli. The mitral valve usually has a cleft and there is evidence of mitral regurgitation through the cleft. When there is a presence of additional small inlet VSD, it is classified as *transitional AVSD*. The *complete AVSD* has a common atrioventricular valve with a single AV valve annulus. Primum ASD and a large inlet VSD are always present and they are contiguous with each other. *Intermediate AVSD* is very similar to complete AVSD except it has two separate right and left AV valve orifices, but the AV valve annulus is common.

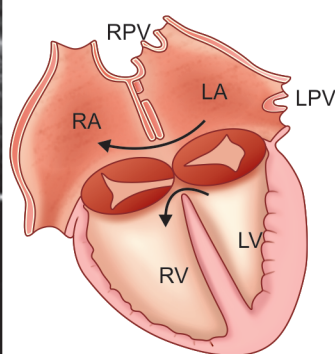
A practical mode of classification depending upon the size of ventricular chambers has practical importance. AVSD is divided



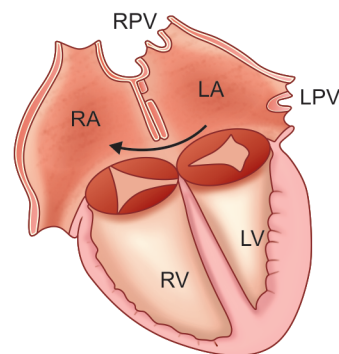
Partial AVSD-primum ASD with separate mitral and tricuspid annuli



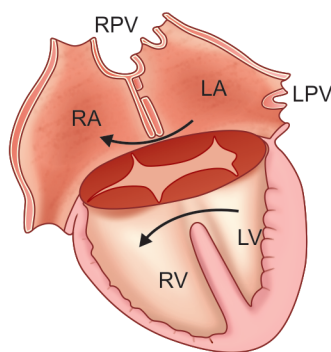
Complete AVSD with primum ASD, inlet VSD, and common valve



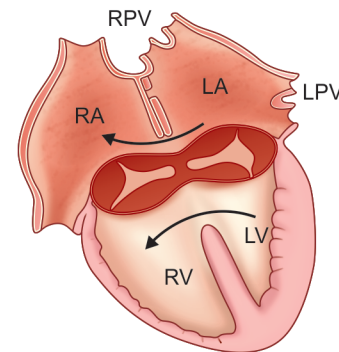
Transitional



Partial



Complete



Intermediate

Figure 1 Morphological classification of atrioventricular septal defect (AVSD)

into *balanced* and *unbalanced* AVSD, if either of the ventricle is hypoplastic. This classification depends upon the attachment of AV valves to the respective ventricles. If one of the ventricles is very small, complete two ventricular repair is not possible. These children eventually undergo univentricular palliation in stages.

PATHOLOGY

Ostium primum ASD is commonly seen in patients with partial AVSD. There is left-to-right shunt across the ASD and there is evidence of mitral or tricuspid valve insufficiency through the clefts of the respective valves. Due to large shunt across the interatrial septal defect, pulmonary arterial pressures are mildly elevated. The physiology of this lesion is therefore similar to that of a large ostium secundum ASD.

As there is a large ASD and a large VSD in complete AVSDs, the left to right shunt occurs at both the levels. Because of excessive pulmonary blood flows pulmonary arterial hypertension is common. In addition to the excessive pulmonary blood flow, the immaturity of lung tissue especially in children with Down syndrome, make them susceptible to increased pulmonary vascular resistance at an early age (Eisenmenger physiology). The ventricles become dilated, if there is AV valve insufficiency.

CLINICAL MANIFESTATIONS

The degree of shunt and AV valve regurgitation determine the clinical features. Virtually, all patients with complete AVSD are symptomatic by 2–6 months of age. Failure to thrive with history of poor feeding, excessive sweating, easy fatigability, fast breathing, chest retractions and recurrent pneumonias occur early in infancy as these shunts have significantly increased pulmonary blood flow. The symptoms worsen in the presence of severe mitral insufficiency. If these symptoms do not develop early, the clinician should suspect premature development of pulmonary vascular obstructive disease.

An uncomplicated primum ASD often is discovered in young children when echocardiography is performed to investigate a murmur. The murmur has typical systolic ejection qualities and is best heard over the upper left sternal border with radiation to the lung fields. The second heart sound is widely split and fixed during respiration. A holosystolic murmur owing to mitral regurgitation through the cleft may be heard at the apex. A low-pitched mid-diastolic murmur can be present. This murmur is secondary to increased flow through the mitral valve orifice.

INVESTIGATIONS

Fetal echocardiography The four chamber view in fetal echocardiography can identify and diagnose AVSD easily and

should be recommended, especially if other anomalies are suggestive of Down syndrome; the parents should be counseled accordingly.

Electrocardiogram (ECG) changes are shown in **Figure 2** and summarized in **Table 1**.

Echocardiography The diagnosis of this anomaly can be done with two-dimensional echocardiography. The apical four-chamber imaging plane clearly visualizes the internal crux. The primum ASD can be diagnosed with apical four chamber view. Usually, the lower atrial septum is absent. The atrioventricular valves are displaced toward the ventricles, with the septal portions inserting at the same level onto the crest of the ventricular septum. The most common abnormality, a cleft, is best visualized from the parasternal and subcostal short-axis imaging planes. In the normal heart, the aortic valve is wedged between the mitral and tricuspid annuli. In AVSD, the aortic valve is displaced anteriorly. This anterior displacement creates an elongated, so-called gooseneck deformity of the left ventricular outflow tract (LVOT). LVOT obstruction may occur in all forms of AVSD (**Figs 3A and B**).

TREATMENT

Surgical correction at an early age, preferably before 6 months of age before the development of pulmonary vascular resistance is undertaken. Medical therapy with diuretics, angiotensin converting enzyme (ACE) inhibitors and digoxin serves to stabilize the patients with large shunt and cardiac failure until surgery.

Table 1 Electrocardiogram (ECG) in atrioventricular septal defect (AVSD)

<i>Superior orientation of the mean frontal QRS axis with left axis deviation (LAD)</i>	
1. Mean QRS axis in the frontal plane (range): -30° to -120°	
Partial AVSD	: Axis direction: -30° and -90°
Complete AVSD	: -90° to -120°
Down syndrome (AVSD)	: Extreme left axis deviation
2. Counterclockwise inscription of the superiorly oriented QRS vector loop. Q wave in leads I and aVL	
3. Biventricular hypertrophy (BVH) or isolated right ventricular hypertrophy (RVH)	
4. Incomplete right bundle branch block—rSR' pattern in leads V3R and V1)	
5. Normal or tall P waves	
6. Sinus rhythm with prolongation of the P-R interval (18–70% of AVSD) due to increased intra-atrial conduction time from high right atrium to low septal right atrium	

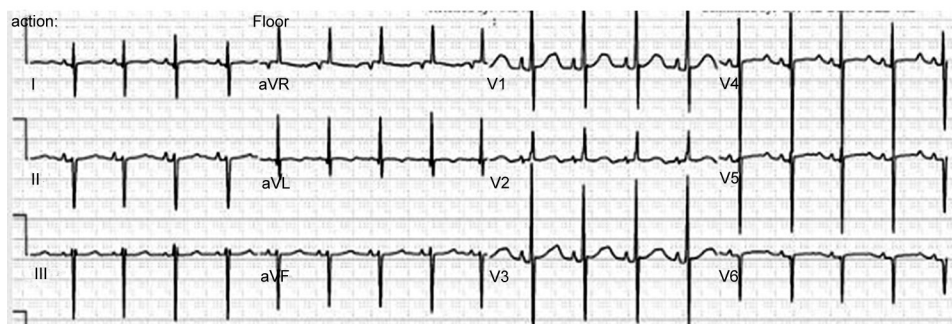
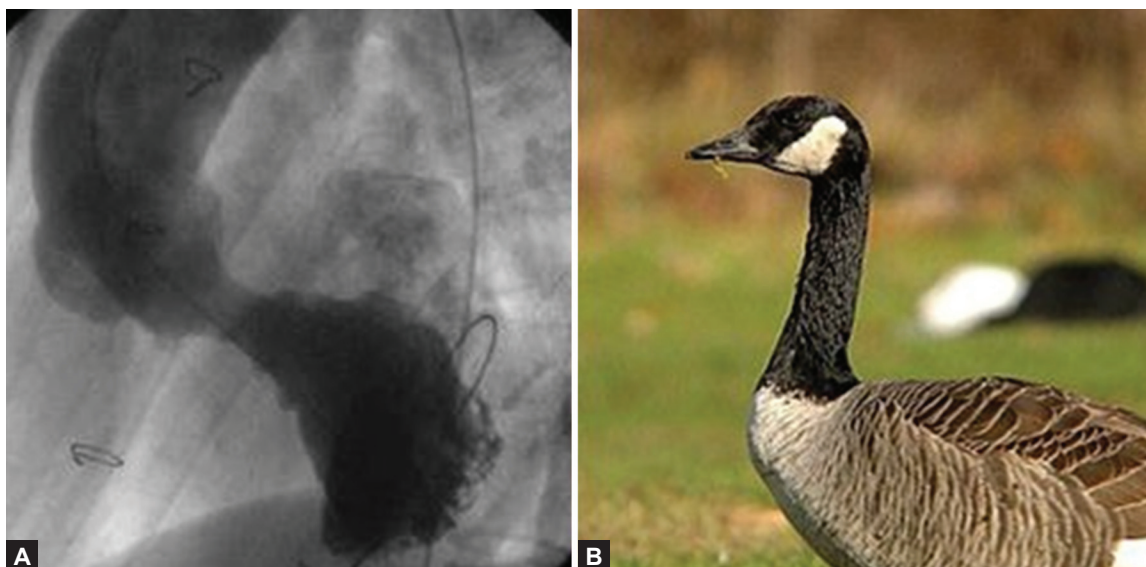


Figure 2 Electrocardiogram (ECG) of a 3-month-old infant with superior axis and right ventricular hypertrophy (RVH)



Figures 3A and B Elongated left ventricular outflow tract (LVOT) simulating a goose neck deformity

In complete AVSD, repair must be done very early, as they have a tendency to develop pulmonary vascular resistance at an earlier age. Surgical correction aims at closure of all the shunts, maintenance of competent AV valves and repair of associated defects. They have near normal cardiac status after surgery. A small percentage of patients may need another surgery for mitral valve repair.

Most of these children become inoperable after 1 year of life due to elevated pulmonary vascular resistance and have a tendency to develop Eisenmenger syndrome (ES) early. Once they develop irreversible pulmonary vascular disease and ES, the natural survival is limited.

The surgical correction of partial AVSD aims at ASD closure and repair of AV valves at about 2–3 years of age. As these lesions behave more such as large ASDs, these children are completely normal after surgical repair. These patients can develop complete AV block, mitral regurgitation and LVOT obstruction after surgery.

MORE ON THIS TOPIC

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IN A NUTSHELL

1. Atrioventricular septal defects are abnormalities of the atrioventricular septum and of the atrioventricular valves. They are also identified as atrioventricular canal defects and endocardial cushion defects.
2. Possibility of complete AVSD should be strongly considered in small infants who present with severe congestive heart failure in early infancy, especially in children with Down syndrome.
3. They should be stabilized initially with antifailure line of treatment. Echocardiography is the key to the diagnosis. Timely diagnosis and early surgical repair before 6 months is very important.

Chapter 40.15

Patent Ductus Arteriosus

K Sivakumar

Patent ductus arteriosus (PDA) refers to a communication between the proximal descending thoracic aorta and the main pulmonary artery. Being essential to be patent in fetal life, it closes within the first few hours to days in all neonates after birth. Persistent patency of the ductus arteriosus (DA) leads to a wide range of hemodynamically significant problems and sometimes even fatal complications such as bacterial endarteritis in postnatal life.

ANATOMY

In most patients with left aortic arch, ductus communication originates from the descending thoracic aorta about 5–10 mm distal to origin of the left subclavian artery and ends in the pulmonary artery confluence. DA starts closing within few hours after birth from the pulmonary end towards the aorta thus resulting in a conical narrow pulmonary end and a wider aortic end (Type A ductus). However, PDA may have varying shapes, some are narrow at aortic end (Type B), some are tubular (Type C), some have mid-ductal constriction (Type D) and the rest have bizarre shapes

(Type E). The significance of its shape gains importance only during planning for interventional duct closure (**Fig. 1**).

Rarely in patients with left arch, the ductus may arise from the right subclavian artery to get connected to the right pulmonary artery. Bilateral ductus are even rarer. In patients with right aortic arch, ductus are common on the left side between left subclavian artery and left pulmonary artery (**Fig. 2**); right side ductus connecting right descending aorta to right pulmonary artery is rarer.

HEMODYNAMICS

Normal Ductal Closure after Birth

Within few hours after birth, the increasing PO_2 of aortic blood causes medial smooth muscle constriction and migration of smooth muscle into the inner wall of the ductus leading to *functional closure*. Infolding of endothelium, disruption of internal elastic lamina, subintimal proliferation, hemorrhage and necrotic edema facilitate later *anatomical closure*. Further, connective tissue proliferation with ensuing fibrosis converts the duct into ligamentum arteriosum. Besides oxygen, the other constricting factors include acetyl choline, catecholamines and bradykinin. Cessation of prostaglandin (PG) production by ductal tissue, withdrawal of placental PG after cord clamp and metabolism of circulating PG by lungs cause constriction of the duct. Preterm ductus are less responsive than term ductus to oxygen and

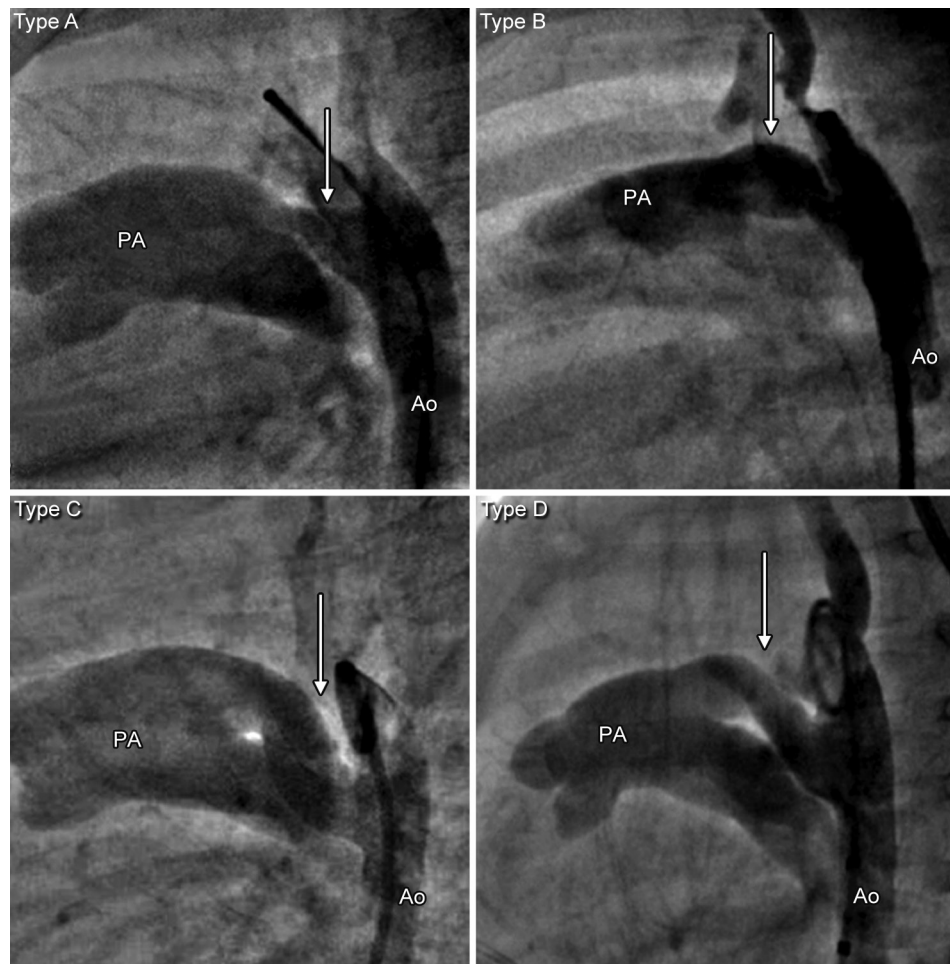


Figure 1 Aortogram in lateral view showing different morphological shapes of PDA: Type A PDA has conical shape with wide aortic end and narrow pulmonary artery end. Type B PDA has wide aortic end and narrow pulmonary artery end. Type C PDA is tubular and Type D PDA has mid-ductal constriction. The classification of ductus by its shape is important in deciding about the method of transcatheter closure
Abbreviations: Ao, aorta; PA, pulmonary artery.

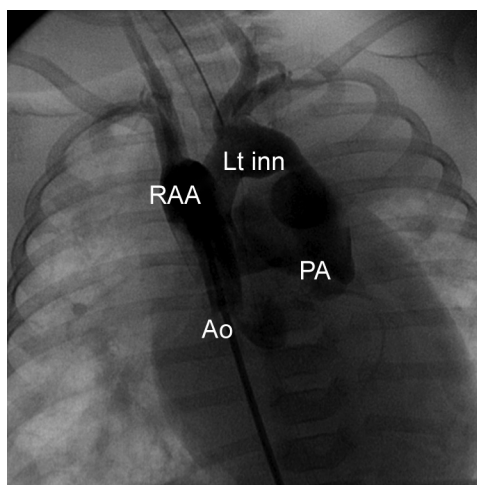


Figure 2 Right aortic arch with left-sided PDA. In patients with right aortic arch, the first arch branch is left innominate artery. PDA arises from either the left innominate artery or left subclavian artery in these patients. It is important to recognize the side of aortic arch before surgical correction

Abbreviations: Ao, aorta; RAA, right aortic arch; Lt inn, left innominate artery; PA, pulmonary artery.

other vasoconstrictors, but are also more sensitive to PG. Premature lungs do not effectively metabolize the PG. So, preterm ductus continues to remain patent for longer period than term babies.

Hemodynamics in Term Babies

In term neonates, the fetal pulmonary resistance continues to remain high for few weeks and this prevents a large left to right shunt. After 1–3 months, with progressive fall of pulmonary vascular resistance (PVR), the patients become symptomatic. The compensatory mechanisms include Frank Starling mechanism in a volume overloaded stretched left ventricular myocardial fiber, progressive left ventricular myocardial hypertrophy, heightened sympathetic activity, all of which increase the left ventricular contractility. This also leads to tachycardia and increased sweating. A large run-off into the pulmonary artery will result in very low aortic diastolic pressure. Tachycardia will also reduce the diastolic period during which coronaries get perfused. This combination of low aortic diastolic pressures, high left ventricular end diastolic pressures and short diastolic period contribute to reduced myocardial perfusion. Prolonged exposure of pulmonary vascular bed to aortic pressures lead to permanent vascular changes, pulmonary arterial hypertension (PAH) and eventually tends to cause reversal of shunt from pulmonary artery to aorta. This results in differential cyanosis with lower limbs more cyanosed than right upper limb, a unique diagnostic feature of ductus with Eisenmenger syndrome. These patients have more exercise induced leg fatigue but less dyspneic compared to other causes of Eisenmenger syndrome. As the ascending aortic saturations are normal, respiratory center and carotid body chemoreceptor are not stimulated.

Hemodynamics in Preterm Babies

Inadequately developed pulmonary arteriolar musculature causes rapid fall of the fetal PVR in preterm. A large shunt increases the pulmonary venous return and increases the left ventricular preload. Preterm left ventricle, with its limited and fewer contractile myocardial architectural components, inadequately responds by Frank-Starling mechanism. Incomplete sympathetic innervation,

low circulating calcium levels, low effective coronary perfusion during diastole in PDA, higher fetal hemoglobin levels associated with low 2,3-diphosphoglycerate (2,3DPG) and more pronounced physiological anemia seen in prematurity reducing the oxygen delivery further to the tissues are all responsible jointly for the onset of early symptomatic heart failure in preterms.

INCIDENCE

In full-term infants, PDA account for 5–10% of all congenital heart defects. Male : female ratio is 1:2. Incidence is six times high in high altitudes. Genetic syndromes associated with PDA are rare, and include Down, Rubinstein-Taybi (broad thumbs, big toe) and Char syndromes (triangular facies with ptosis, short philtrum and patulous lips, abnormal fifth finger, supernumerary nipple). Maternal rubella infection is a known teratogen in the first trimester of pregnancy. It is important to realize that PDA in term babies is a structural abnormality, but in preterms, it is just a physiological developmental problem. In preterms, PDA occurs in 8 out of 1,000 babies. The incidence is proportional to the degree of prematurity. It is 45% in preterms weighing less than 1,750 g at birth, 80% in preterms with less than 1,250 g weight and almost invariably seen in all preterms with less than 1,000 g birthweight when associated with lung disease.

CLINICAL FEATURES

Symptomatology

The diameter and length of the duct, relative resistances of the pulmonary and systemic arterial bed determine the degree of shunt from aorta to the pulmonary artery. Narrower and longer ducts offer more resistance to flow of blood. Large window such as ducts with short lengths will transmit entire aortic pressures to pulmonary arteries and lead to elevated pulmonary artery pressures. Symptoms in PDA depend on the degree of shunt and the myocardial ability to handle the resulting volume overload. While gross heart failure and recurrent pneumonias are seen in very large ductus, moderate ductus causes mild growth retardation and effort intolerance. The symptoms are minimal as long as the myocardial hypertrophy compensates for the volume overload without undue increase of left ventricular end diastolic pressures.

Examination Findings

Peripheral pulses—radials, dorsalis pedis, are bounding with wide pulse pressures once the left to right shunt gets established after fall of the neonatal PVR. Pulse rates are higher in infants with heart failure, who tire out easily, sweat profusely and thrive poorly. Precordium is hyperkinetic, proportionate to the left ventricular volume overload. The characteristic auscultatory finding is Gibson's continuous murmur, characterized by late systolic peaking and continuation through the second sound into the diastole. There are multiple crackling eddy sounds in the murmur, which vary from beat to beat and give the murmur a machinery quality. This is absent in most other causes of continuous murmurs such as venous hum, coronary arteriovenous fistulae and ruptured sinus of Valsalva aneurysm. These eddy sounds are caused by coalition of two jets hitting in opposing direction, one antegrade from pulmonary outflow and other retrograde from duct into the main pulmonary artery. In infants with gross heart failure due to very large PDA, murmur may be present only in systole. The masking of the diastolic component of the murmur is due to very low flows from aorta to pulmonary artery in diastole due to complete equalization of diastolic pressures between aorta and pulmonary artery. Second sound may be paradoxically split due to prolonged left ventricular ejection, but is difficult to appreciate in the continuous murmur. In Eisenmenger syndrome, the split becomes closer, but again widens, if right ventricle fails later.

NATURAL HISTORY

Ductus arteriosus seldom closes beyond early infancy. Spontaneous closure in later age may be due to endocarditis or thrombus. Sometimes a closed ductus may reopen due to rupture of valve such as membrane or dissection of the duct. Moderate to large ductus in term babies become symptomatic after 4–6 weeks of life once the fetal PVR falls. If the left ventricle fails to cope with the volume overload caused by the large shunt, the infants become very sick to need urgent interventions. Dilated left atrium may obstruct left lung airway and cause hyperinflation or collapse of the lungs and lead to pneumonia. After 3–6 months, progressive left ventricular myocardial hypertrophy causes compensation of the heart failure and symptoms tend to improve.

In untreated large ductus, beyond 18 months of age, pulmonary vascular changes may begin to appear and symptoms slowly subside. Differential cyanosis starts to appear initially on exertion and later at rest. Infective endarteritis may be diagnosed with vegetations in the pulmonary end of the duct. Ductal aneurysms may sometimes be incidentally detected or associated with hoarse voice secondary to recurrent laryngeal neuroparaxia. Aneurysms may rupture, dissect, form thrombus that embolize, get infected, compress left pulmonary artery or left bronchus, and rarely present with hemoptysis or hematemesis. Calcification may occur in adult life, pose problems for surgical ligation and division. Sudden deaths in adults are due to rupture or dissection.

DIAGNOSIS

Chest X-ray

Cardiomegaly, dilated main pulmonary artery segment, increased lung vascularity are proportional to the shunt. Unlike ventricular septal defect, aortic knuckle will also be prominent (**Figs 3A and B**). Young infants with heart failure show pulmonary venous hypertension, interstitial opacities causing hilar haze. Dilated left atrium may lead to collapse or hyperinflation of the lower lobe of left lung. Rare findings include ductal aneurysm causing abnormal bulge on left heart border and ductal calcification in adults.

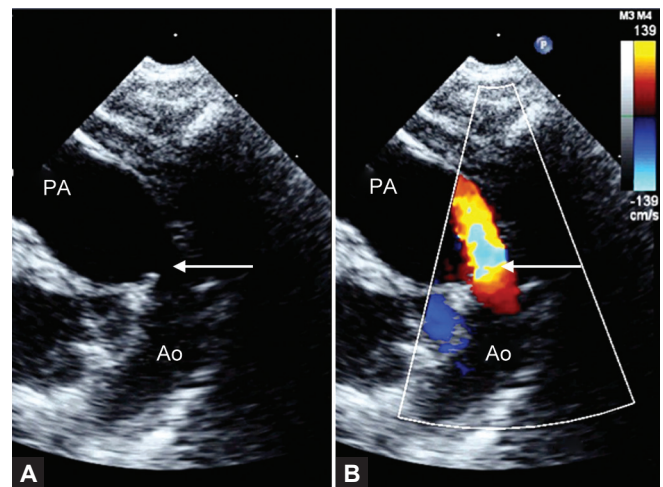
Electrocardiogram

Mean QRS axis is normal, except in rubella syndrome where superiorly directed QRS axis may be noted. Left ventricular forces

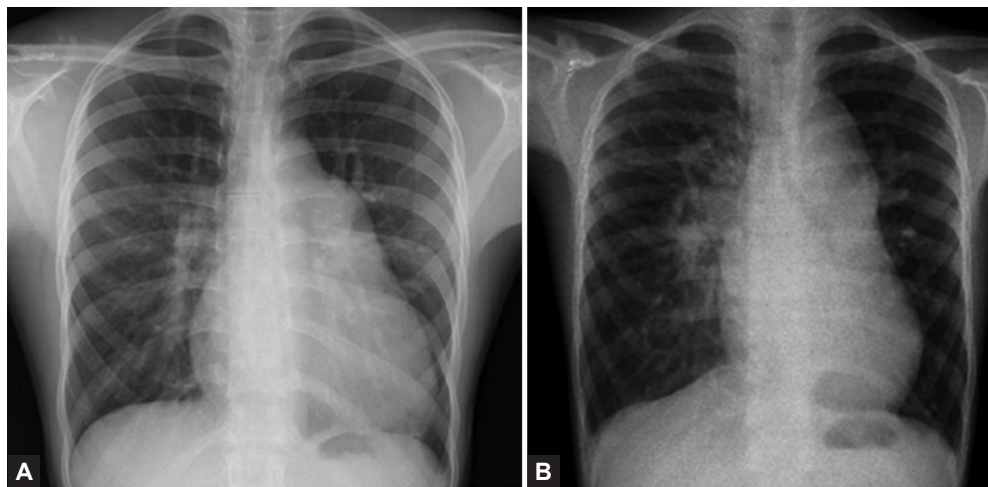
may dominate and lead to deep Q waves in V6 with tall upright T waves. Left atrial enlargement may be seen. Pulmonary vascular disease may shift the QRS axis to right and lead to prominent right ventricular forces and right atrial enlargement. PR segment is prolonged in 10–20% patients.

Echocardiogram

Most important utility of echocardiogram in a child with classical continuous murmur of PDA is to exclude a duct dependent lesion such as pulmonary atresia where a duct should never be closed. The hemodynamics of the PDA will be shown by left atrial and ventricular enlargement, gradient across the PDA on continuous Doppler trace, flow reversal in abdominal aorta in diastole. Anatomy of the PDA, its size at aortic and pulmonary end, its shape, absence of coexistent posterior ductal shelf (causing coarctation of aorta) are important findings to plan interventional nonsurgical transcatheter PDA closure (**Figs 4A and B**).



Figures 4A and B (A) Echocardiography in PDA in ductal view shows large tubular communication shown by arrow between the descending aorta (Ao) and pulmonary artery (PA) and (B) Color Doppler flows across the PDA from aorta to pulmonary artery



Figures 3A and B Chest X-ray in PDA. In large ducts with large left to right shunt (A), there is cardiomegaly, dilated main pulmonary artery segment, plethoric lung fields, dilated aortic knuckle. When the pulmonary vascular resistance increases to lead to reversal of shunt as in Eisenmenger syndrome (B), there is more dilatation of the central pulmonary arteries and pruning of the vasculature in the peripheral one-third of the lung fields

Cardiac Catheterization Hemodynamics

The utility of catheterization is resorted to assess the hemodynamic characteristics of the shunt in patients with features of high PVR (Table 1).

TREATMENT

Medical Management of Preterm PDA

Urgent treatment is resorted to, if there is respiratory distress, apnea, heart failure, splanchnic ischemia and necrotizing enterocolitis due to aortic run-off. Packed cell transfusion to improve oxygen carrying capacity; it reduces the HbF concentration and improves tissue oxygen delivery. Other steps include sodium and fluid restriction, diuretics and dopamine for inotropic effect.

Pharmacological closure Indomethacin orally or intravenously at dose of 0.2 mg/kg is given unless, there is severe renal failure, bleeding or manifest necrotizing enterocolitis. Alternatives to indomethacin are ibuprofen (less incidence of renal failure), oral propranolol and oral paracetamol. In patients who fail these medications, surgical ligation after thoracotomy, thoracoscopic clipping and transcatheter device closure are done.

Management of Term PDA

In symptomatic PDA, early treatment is warranted. In severe heart failure, stabilization with diuretics, inotropes and ventilation may be needed. Definitive treatment involves transcatheter closure or surgical closure.

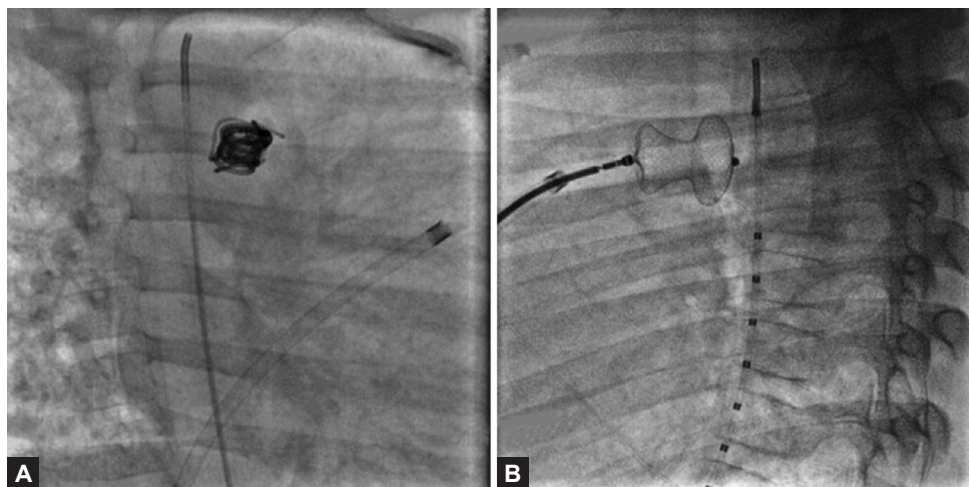
Transcatheter closure is done through femoral artery or venous access with platinum embolization coils with Dacron fibers or ductus occluder devices, which are nickel-titanium alloy wire mesh occluders with polyester fabric inside the mesh (Figs 5A and B).

Table 1 Management decision for PDA based on cardiac catheterization hemodynamics

<p>Contraindications for ductus closure</p> <ul style="list-style-type: none"> Severe PAH with the following catheter hemodynamic data 	<ul style="list-style-type: none"> Step down of oxygen saturations from ascending aorta to descending aorta is more than 2% Oxygen saturations in femoral artery is below 92% irrespective of the ascending aortic saturations Pulmonary vascular resistance exceeds 8 Wood units No substantial improvement of vascular resistance on oxygen or vasodilators such as nitric oxide and No discernible fall in pulmonary artery pressures with test balloon occlusion of ductus
<p>Justifiable indications for ductus closure</p>	<ul style="list-style-type: none"> Step-up from right ventricle to pulmonary artery over 5% Qp/Qs ratio of more than 1.5
<p>There are some practical difficulties in oximetry since the stream of blood from aorta through the duct may stream into one or the other pulmonary artery.</p>	

Abbreviation: PAH, pulmonary arterial hypertension.

Surgical treatment is done with ligation through left thoracotomy (carries risk of recanalization), triple ligation or ligation and division (eliminates risk of recanalization) or thoracoscopic clipping of ductus. PDA surgical closure is often performed by closed heart surgery; but some calcified ductus in adults may need surgery on cardiopulmonary bypass. In hypertensive ductus with elevated PVR, medical therapy with sildenafil, bosentan is indicated.



Figures 5A and B Interventional closure of PDA in cardiac catheterization laboratory can be done without surgical incisions through femoral venous or arterial cannulation. They are done with coils (A) or nitinol occluder devices (B)

IN A NUTSHELL

1. Patent ductus arteriosus is a structural abnormality in term babies, but a physiological developmental disadvantage in preterms.
2. Shunting across PDA depends on size of the duct, relative differences between the pulmonary and systemic vascular resistances.
3. Continuous murmur peaking around the second sound with eddy sounds is hallmark of PDA with large left to right shunt.
4. Spontaneous closure of PDA in term babies is very rare and will need closure.
5. Most preterm ducts are managed by conservative medical therapy.
6. Nonsurgical closure of PDA has emerged to be safer and more attractive alternative to surgery.
7. Late problems of uncorrected PDA include pulmonary hypertension, shunt reversal, ductal calcification, aneurysm and endocarditis.

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Chapter 40.16

Anomalous Left Coronary Artery from Pulmonary Artery, Coronary Arterial Fistula and Ruptured Sinus of Valsalva

MS Ranjith

ANOMALOUS LEFT CORONARY ARTERY FROM PULMONARY ARTERY

Anomalous left coronary artery from pulmonary artery (ALCAPA) is a rare but important anomaly as it is treatable and long-term outlook is excellent if recognized and referred early for surgical repair. Incidence is 1:250 to 1:400 of all congenital cardiac defects with a male preponderance. ALCAPA is usually an isolated anomaly although rarely symptoms may be prevented by presence of a patent arterial duct or a ventricular septal defect.

Pathophysiology

In fetal life there are no effects; postnatally in the first few weeks, pulmonary artery (PA) pressures remain elevated with some admixture at the oval fossa and ductal levels, therefore increased extraction by the myocardium compensates. As PA pressure falls the left coronary artery (LCA) is perfused by desaturated blood at low pressures. Left ventricle (LV) with huge oxygen demand becomes ischemic. LV function becomes progressively impaired. Simultaneously collaterals develop from the right coronary artery (RCA) which arises normally from the aorta, to the LCA. This determines the presentation, as ischemic damage varies depending on the collateralization. Therefore, adults may present with a perfect set of collaterals and good LV function, while young infants may have poor collaterals and severe ischemic damage.

Hemodynamics

The RCA enlarges as collaterals develop while the LCA remains small. With extensive collaterals, the LV remains well-perfused while with poorly developed collaterals, the LV becomes ischemic, dilated, dilated and fibrotic. Mitral regurgitation develops both due to annular enlargement as the LV dilates and due to papillary muscle involvement in the ischemic process. Left atrium then enlarges with increase in pressures leading to pulmonary venous congestion.

Clinical Features

Infants may present with symptoms of congestive cardiac failure (CCF). Others have incidental detection of cardiomegaly on the chest X-ray (CXR). Murmur of mitral regurgitation or a gallop rhythm may be noted. Presentation as a *dilated cardiomyopathy* is frequent and an electrocardiogram (ECG), CXR or echocardiogram may reveal the diagnosis. Some infants present with the typical *bland white and garland* syndrome of ischemic angina episodes brought about when feeding, stress or defecation; the infant is then severely distressed with grunt, diaphoresis, distress and crying. These symptoms are mistaken for a colic or reflux.

Features of CCF are evident in some with respiratory distress, hepatomegaly and mitral regurgitation murmur or a gallop rhythm and an apical mid-diastolic rumble. Pulses are small volume with tachycardia. Apex is displaced down and out. Sometimes an

angina episode is witnessed but rarely recognized. The older child with good collaterals may have normal cardiac findings. Excessive collaterals may cause a continuous murmur resembling a patent arterial duct.

Investigations

Electrocardiogram Sinus tachycardia with ventricular ectopic beats, ventricular tachycardia and pathologic Q waves as well as ST segment and T wave abnormalities are seen in leads I, AVL, V5, V6 typical of anteroseptal myocardial infarction in sick infants with CCF. In some the ECG changes evolve with time. ECG may not be normal but may not be diagnostic on occasion. Older child with good collaterals may have a normal ECG.

Chest X-ray The sick infant may have cardiomegaly in varying degrees depending on extent of infarction and mitral regurgitation with left atrial enlargement and pulmonary venous congestion. The older child with good collaterals may have a normal CXR.

Echocardiography and Doppler In sick infants, left ventricular dilatation with poor contractility and varying degrees of mitral regurgitation is noted. Often misdiagnosed as dilated cardiomyopathy if the echocardiographer does not pay attention to the coronary arteries. Careful evaluation will demonstrate a dilated RCA and the LCA origin from the PA, often with reverse flow on color from the LCA to the PA.

Others Thallium 201 scintigraphy shows *cold areas* in affected myocardium, but is nonspecific and can occur in cardiomyopathy. Cardiac catheterization is seldom required unless ECG is atypical and echocardiogram inconclusive especially in the older child. Selective right coronary angiogram clearly demonstrates the left coronary artery filling from collaterals arising from the RCA, and often filling the PA. Computed tomography [(CT) angiography] is a better noninvasive alternative in this setting.

Natural History

Left untreated, some will stabilize with collateral development and survive to adult life to develop symptoms then but overall outlook is poor with death due to arrhythmia, CCF, cardiogenic shock in a majority.

Management

Medical management is to stabilize the child for surgery with inotropic support and afterload reduction using nitroglycerin. Digoxin is best avoided due to arrhythmogenicity. Morphine for pain and anxiety, ventilation and paralysis are required for the very sick.

Cornerstone of treatment is surgery. Early surgery at diagnosis offers the best prospect for the patient. Early procedures included ligation of the left coronary artery, internal mammary artery or subclavian artery graft. These are obsolete now. Direct reimplantation of the LCA from the PA to the aorta with a button of PA around the origin, is the modality of choice. In some instances of difficult coronary transfer, the Takeuchi procedure is applied; here an aortopulmonary window is created and a baffle used in the PA to direct aortic blood to the LCA. The sickest infants with severe LV dysfunction often require postoperative support with ventricular assist devices.

CORONARY ARTERY FISTULA

These are distal communications from the coronary artery, usually the right coronary artery (RCA) to a cardiac chamber or vessel. This can be to the superior caval vein, right atrium, right ventricle, PA, left atrium or to the left ventricle. Embryologically these fistulae represent remnants of the coronary to intramyocardial sinusoidal circulation.

These may be simple direct connections from a coronary to the chamber or vessel or a complex multiple communications. Some communications can be large with significant shunting of blood. They enlarge with time. These fistulae cause *steal* from the myocardium with ischemia, or present with a continuous murmur or as endocarditis. They can often rupture.

Most are asymptomatic and diagnosed incidentally when evaluating a murmur or cardiomegaly noted on CXR. Some large ones can present with CCF in infancy. Others can have exercise intolerance, angina, dyspnea or rarely arrhythmias. They often present with a continuous, patent arterial duct like murmur, which is heard lower down and appears superficial and louder in diastole rather than in systole. ECG has no characteristic findings. CXR may show cardiomegaly. Echocardiography and color Doppler helps display the origin, course and entry points of these fistulae and show multiple fistulae when present.

Treatment can be surgical ligation of these fistulae and increasingly coil embolization or even device closure.

ANEURYSM OF SINUS OF VALSALVA AND RUPTURED SINUS OF VALSALVA

A localized weakness of the wall of a sinus of Valsalva leads to aneurysmal bulging and eventual rupture. These localized aneurysms are usually congenital but may follow infective endocarditis. They occur just above the aortic leaflet hinge point. A majority occur in the right aortic sinus. Up to 50% of these are associated with doubly committed and juxtarterial ventricular septal defects (VSD) or outlet muscular VSDs. Progressive prolapse of the aortic valve leaflets leads to aortic regurgitation (AR), which is usually progressive.

Because the aortic root is a central structure, they can rupture into any cardiac chamber. Usual ruptured sinus of Valsalva (RSOV) is to the right ventricle especially when associated with a VSD. Less commonly the rupture is to the right atrium. Unruptured aneurysms can obstruct the right ventricular outflow, obstruct a coronary, cause heart block due to compression of the conducting system.

Ruptured sinus of Valsalva seldom presents in infancy or early childhood. RSOV to the right ventricle or atrium produces a left to right shunt of varying magnitude. Endocarditis occurs in 5–10%.

Unruptured aneurysms are diagnosed incidentally during routine echocardiograms or angiography for other conditions. Rupture may cause chest or abdominal pain and symptoms of CCF may develop in larger ruptures. There may be a loud continuous murmur resembling a patent arterial duct, but occurring lower

down. AR murmur and an associated VSD murmur may produce confusing findings.

Electrocardiogram may be normal or show chamber hypertrophy with large ruptures. CXR will show enlargement of the chambers ruptured into. In addition, PA dilatation and pulmonary plethora may be noted. Echocardiography and color Doppler as well as transesophageal echocardiography show the details of the aneurysm, site of rupture, presence and severity of AR. Associated VSD will also be seen as well as the hemodynamic effects. CT angiography and magnetic resonance imaging can add to provide good definition of the lesions. Cardiac catheterization and angiography is seldom required nowadays with excellent resolution using other modalities of imaging.

Treatment is primarily surgical repair. Device closure of the RSOV is done but with a risk of further damaging the aortic valve. At surgery the aortic valve can be repaired for the AR or the VSD closed when present.

IN A NUTSHELL

1. Anomalous left coronary artery from pulmonary artery (ALCAPA) may present with ischemia, CCF, incidental cardiomegaly, or as dilated cardiomyopathy. Left untreated, overall outlook is poor with death due to arrhythmia, CCF, cardiogenic shock in a majority. Cornerstone of treatment is surgery.
2. Coronary artery fistulae (CAF) are distal communications from the coronary artery, to a cardiac chamber or vessel. They enlarge with time. These fistulae cause *steal* from the myocardium with ischemia, or present with a continuous murmur or as endocarditis. They can often rupture. Treatment is surgical ligation.
3. A localized weakness of the wall of a sinus of Valsalva leads to aneurysmal bulging and eventual rupture. Rupture may cause chest or abdominal pain and symptoms of CCF may develop in larger ruptures. Treatment is surgical.

MORE ON THIS TOPIC

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Chapter 40.17

Pulmonary Stenosis

Shreepal Jain, Bharat Dalvi

Congenital pulmonary stenosis (PS) may occur at, above or below the valve. It may occur as isolated lesion or in association with other congenital heart defects (CHDs) in up to 25–30% of all congenital heart diseases (CHDs).

VALVAR PULMONARY STENOSIS

Epidemiology

First described by Morgagni in 1761, valvar PS (V-PS) is one of the common CHDs. Although usually isolated, it may be associated with other CHDs such as atrial septal defect (ASD), ventricular septal defect (VSD), and persistent ductus arteriosus (PDA), tetralogy of Fallot (TOF), transposition of great arteries (TGA), double outlet right ventricle (DORV), etc.

Incidence

Valvar PS constitutes 7% of all CHDs accounting for 80–90% of all lesions with right ventricular outflow tract (RVOT) obstruction. It has higher birth prevalence in Asia as compared to Europe and the USA.

Epidemiology and Etiology

There is no specific sex predilection. In isolated PS, the recurrence risk is reported to be 1.7–3.7%. In syndromic PS, the recurrence risk is higher, depending on the inheritance pattern.

Valvar PS occurs frequently in patients with Noonan syndrome, less frequently in Williams-Beuren syndrome, neurofibromatosis and occasionally with 22q11 deletion syndrome. It has been described in Alagille and congenital Rubella syndrome although peripheral pulmonary arterial stenosis (PPS) is the more usual association.

Embryogenesis

Development of semilunar valves requires the formation of endocardial cushions in the cardiac outflow tract and remodeling of these cushions into valve leaflets. Mechanisms of the valve elongation process involve differential proliferation and apoptosis of cushion mesenchymal cells, as well as tissue-tissue interactions among mesenchymal cells, endocardial cells, and myocardial cells, the latter originating from the secondary heart field (SHF). *Calcineurin/Nfatc1* signaling in SHF is essential for semilunar valve development. The absence of SHF calcineurin causes increased apoptosis of conal cushion mesenchyme, leading to failure or abnormal development of semilunar valves.

Pathology

The most common of the two types is the classical or typical valvar PS characterized by a normal sized valve annulus and a thin, pliant or dome-shaped membrane with three well-defined but incomplete raphae extending from the central narrow opening (Fig. 1). Obstruction is mainly secondary to incomplete opening of the leaflets. There is associated poststenotic dilatation of the main pulmonary artery (MPA) usually extending into the left PA (LPA) that may be secondary to high velocity jet hitting the PA after ejecting through the small valve orifice. The degree of dilatation does not correlate with the severity of obstruction and is often more pronounced in mild cases.

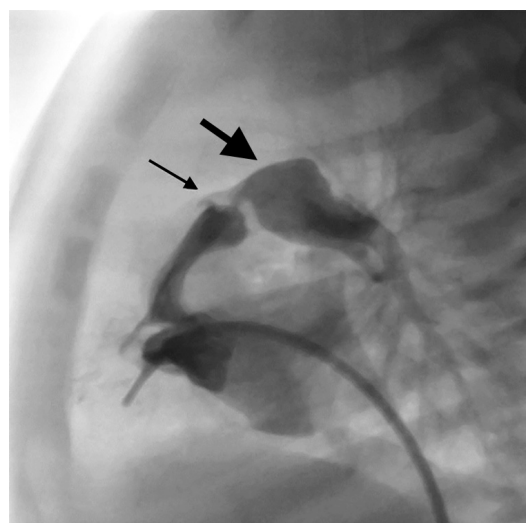


Figure 1 Right ventricular angiogram in lateral view demonstrating a typical doming pulmonary valve with thin leaflets (thin arrow) and narrow jet of flow across it along with poststenotic dilatation of the main pulmonary artery (thick arrow)

Dysplastic pulmonary valve, seen in up to 20% of patients, is characterized by hypoplastic annulus, three distinct thick immobile cusps without any commissural fusion. There is usually no poststenotic dilatation of the MPA. It is commonly seen in patients with Noonan syndrome. Obstruction is mainly due to immobility of the thick leaflets.

Moderate and severe degree of stenosis is associated with right ventricular hypertrophy (RVH). Localized hypertrophy of the infundibular region develops in some producing subvalvar obstruction. Tricuspid valve (TV) annulus is usually normal sized but may enlarge with development of right ventricle (RV) failure. Right atrium (RA) is dilated and hypertrophied in severe cases.

Hemodynamics

Right ventricle myocardium normally receives flow throughout cardiac cycle since aortic pressure always exceeds RV pressure. In longstanding moderate to severe PS, systolic flow to RV is reduced causing subclinical infarction and subendocardial fibrosis.

Although a hypertrophied RV is initially able to maintain normal stroke volume, it eventually dilates and fails. With fall in stroke volume, tissue oxygenation during periods of increased demand is maintained by increased oxygen extraction by peripheral tissues leading to widening of arteriovenous oxygen difference (AVO_2) and peripheral cyanosis. In those with a patent foramen ovale (PFO) or ASD, cardiac output might be maintained via right to left shunt at atrial level at the cost of desaturation.

Critical Pulmonary Stenosis

Neonates with critical PS are characterized by severely hypertrophied RV with hypoplastic cavity, systemic or suprasystemic RV pressures, central cyanosis secondary to right to left atrial shunt across the PFO and duct dependent pulmonary blood flow.

Clinical Features

Symptoms

Majority of children with PS are diagnosed due to incidental detection of a murmur. Those with long standing moderate to severe stenosis present with exertional dyspnea and fatigue. Patients with untreated severe PS have exercise-induced chest

pain, syncope or even sudden cardiac death. Occasionally, they present with generalized anasarca secondary to RV dysfunction. Neonates with critical PS present with severe cyanosis at birth and may develop severe hypoxia and acidosis with PDA closure.

Signs

Growth and development is usually normal except in those with Noonan or Rubella syndrome. Typical facies may be seen in Williams, Noonan and Alagille syndromes. Central or peripheral cyanosis may be detected for reasons described earlier. Peripheral pulse is usually normal in mild-moderate cases and may be reduced in severe PS with RV failure. The *a* wave in jugular venous pressure (JVP) tends to be progressively larger with increasing severity of PS due to stronger atrial contraction. With development of tricuspid regurgitation and RV failure, the *v* wave becomes more prominent with a brisk *y* descent.

Palpation may reveal RV systolic impulse along the left parasternal border. In moderate and severe PS, there may be a palpable thrill in the second left intercostal space (LICS), radiating upwards and towards the left.

On auscultation, *S*₁ is usually normal. This is immediately followed by a high-pitched, sharp pulmonary ejection click (PEC), heard maximal in the second left intercostal space (LICS). The click is not heard in those with dysplastic valve. *S*₁-PEC interval decreases with increasing severity of PS and PEC may be difficult to separate from *S*₁ in severe PS. Intensity of PEC decreases with deep inspiration and increases on expiration. *S*₂ in PS is usually split, with the degree of splitting being proportional to the severity of stenosis. The split may become fixed in severe stenosis as a result of a fixed stroke volume. Pulmonary component (*P*₂) tends to become softer with increasing severity, making split difficult to appreciate. A fourth heart sound (*S*₄) is often heard at the lower left sternal border in patients with severe PS.

Murmur is ejection systolic type heard maximally in second LICS and radiating upwards and to the left. In mild PS, the murmur peaks in mid-systole and ending at or before the aortic component of second heart sound (*A*₂). With increasing severity, the peak tends to occur later in systole and even extending beyond *A*₂.

Neonates with critical stenosis tend to have softer systolic murmur as a result of reduced right ventricular output across the pulmonary valve. *P*₂ is usually not audible in such cases.

Investigations

Electrocardiogram

In mild PS, rightward QRS axis or an upright T wave in V1 may be the only finding in an otherwise normal looking electrocardiogram (ECG). Right axis deviation (RAD), R : S ratio in lead V1 more than 4 : 1 and R more than 20 mm are common findings in moderate PS. With severe stenosis, further RAD, monophasic R wave in lead V1 and deep S waves in the left precordial leads, with an R : S ratio less than 1 in V6, can be seen. Inverted T waves can be seen in II, III, aVF and right precordial leads. T wave inversion in the precordial leads beyond V3 is suggestive of suprasystemic RV pressure. In patients between 2 years and 20 years, a rough estimate of the RV systolic pressure can be obtained if there is a pure R wave in lead V1 or V_{4R} by multiplying its height (in millimeters) by 5.

In those with critical PS or severe PS with hypoplastic RV cavity, the QRS axis tends to more leftward than expected (+30° to +70°) with evidence of left ventricular hypertrophy. These neonates or infants have adult progression of R-wave in precordial leads. Infants with Congenital Rubella and Noonan syndrome may have left axis deviation of the QRS complex.

Radiology

Cardiac size is usually normal except in cases with tricuspid regurgitation (TR) and RV failure or in neonates with critical PS (**Fig. 2**). Most notable finding is a prominent main PA segment secondary to poststenotic dilatation. Pulmonary vascularity is normal unless reduced by development of RV failure or large right to left atrial level shunt in critical PS.

Echocardiogram

A two-dimensional echocardiogram (2DE) is now the investigative modality of choice for confirming the diagnosis of PS. It can help in differentiating a typical doming PS valve with thin leaflets from a thick, dysplastic valve. In addition, secondary changes like poststenotic PA dilatation, RVH, infundibular hypertrophy and tricuspid valve (TV) anatomy and function can be assessed. Color Doppler echocardiography adds to the information by exactly locating the origin of flow turbulence, whether valvar, subvalvar or supravalar. Other information like flow across any atrial level shunt can also be identified. Severity of stenosis can be estimated by Doppler interrogation of the jet across the pulmonary valve using the simplified Bernoulli equation.

Cardiac Catheterization and Angiography

With the advent of echocardiography, catheterization is now mainly reserved for interventional purpose. Important hemodynamic information that can be obtained includes RV systolic pressure, which can be compared with the systemic systolic pressure and the gradient across the pulmonary valve. In addition, presence of infundibular component can be detected with the help of an end-hole catheter. PA pressure is usually normal or may be low in severe PS with RV dysfunction. Elevated RV end diastolic pressure is suggestive of severe RV hypertrophy with diastolic dysfunction. RA pressure is usually normal unless there is associated RV failure or significant tricuspid regurgitation.

RV angiogram provides information about the valve morphology, annulus size, presence or absence of poststenotic dilatation of PA, infundibular component (fixed versus dynamic), RV cavity size and function, and TV function.

Differential Diagnosis

Conditions mimicking mild PS include innocent or functional murmurs, ASD, idiopathic dilatation of PA, mitral valve prolapse,

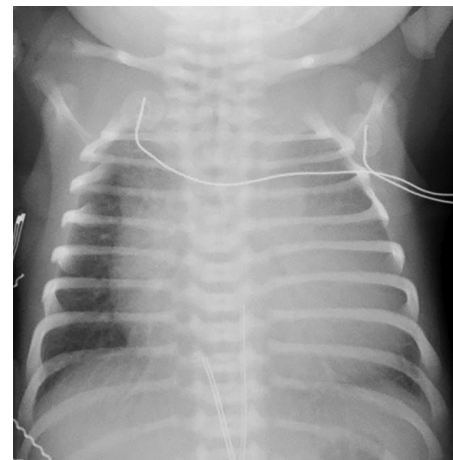


Figure 2 Chest radiograph in a newborn with critical pulmonary stenosis depicting cardiomegaly with dilated right atrium. Radiographic appearance may be similar to that seen in a neonate with Ebstein anomaly

and mild aortic stenosis. Moderate and severe PS need to be differentiated from small to moderate sized VSD and moderate to severe AS. Neonatal critical PS needs to be differentiated from Ebstein anomaly with functional pulmonary atresia and pulmonary atresia with intact ventricular septum.

Management

Balloon Pulmonary Valvuloplasty

Balloon pulmonary valvuloplasty (BPV) is the procedure of choice for moderate and severe PS with typical doming pulmonary valve as well as the initial therapy for dysplastic valve. With advancement in catheter and balloon hardware, it is now possible to treat even newborns with critical PS with good results. Balloon diameter is chosen as 1.2–1.4 times the angiographically measured pulmonary annulus size. Mechanism of obstruction relief involves commissural splitting after balloon inflation (**Figs 3A and B**). As a result, pulmonary regurgitation (PR) is a natural consequence of the procedure and an indirect indicator of adequate dilatation. Pullback pressure recording with an end-hole catheter is done after the dilatation to assess the amount of relief. Occasionally some residual gradient may be noted across the infundibular region. This dynamic gradient resolves once the hypertrophied infundibular muscle regresses. Rarely, β -blocker treatment is necessary to relieve this dynamic obstruction after BPV.

As per the American Heart Association scientific statement, Class I indications for BPV include critical PS and valvar PS with catheter measured or echocardiographically measured peak instantaneous gradient of more than or equal to 40 mm Hg or clinically significant valvar PS with evidence of RV dysfunction.

At midterm follow-up (< 2 years), restenosis is observed in 8–10% of patients. In the absence of severe annular hypoplasia and valvar dysplasia, this can be treated with a repeat BPV using a larger balloon with good success rates. In the long-term follow-up, the freedom of reintervention is reported as 88% and 84% at 5 and 10 years, respectively. Reported incidence of adequate obstruction relief in those with dysplastic valve ranges from 35% to 65%.

In newborns with critical PS, immediate effective gradient reduction is achieved in more than 90% patients. However, 5–10% patients are unable to maintain adequate forward flow across the pulmonary valve. Usually these babies can be maintained on

prostaglandin E1 infusion for providing adequate pulmonary blood flow (PBF) before gradually weaning it. However, a stable source of PBF in the form of surgically created aortopulmonary shunt or a transcatheter PDA stenting may be required if they are unable to be weaned even after 2–3 weeks. Another 10% may require repeat BPV within months of the initial procedure.

Incidence of moderate PR after BPV ranges from 5% to 24%. Incidence of moderate to severe PR appears to increase over period of time. Moderate or severe pulmonary insufficiency developed in 74% of patients who underwent the procedure as neonates, in contrast to 44% of all other patients. Longstanding moderate to severe PR has deleterious effects on RV function and exercise tolerance as well as increased incidence of arrhythmias. Such patients may need a pulmonary valve replacement (PVR) to minimize these risks.

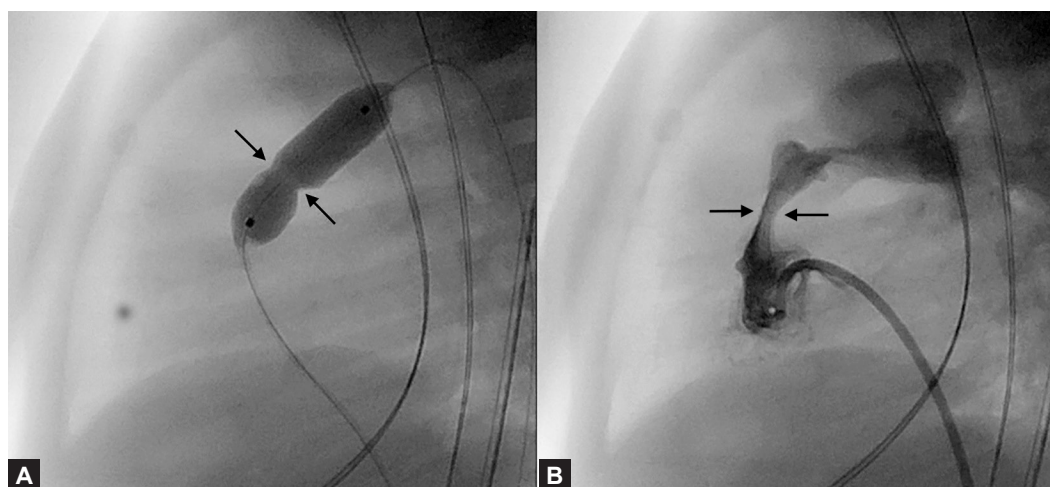
In experienced hands, risk of procedure related death (0.24%) or major complications (0.35%) are very low. Complications, including transient bradycardia and hypotension during balloon inflation, transient or permanent right bundle branch block or atrioventricular block, balloon rupture, tricuspid valve chordae/papillary muscle rupture, and tears in the pulmonary artery have been reported, but rarely.

Surgical Valvotomy

Surgery is now reserved for only those with dysplastic valves with inadequate relief after BPV or those with multiple levels of obstruction. Adequate relief of obstruction often necessitates complete removal of the valve annulus and leaflets and insertion of transannular patch. As a result, moderate to severe PR is common in such patients. Restenosis rate is very low with up to 96% remaining free of reintervention at 10 years follow-up.

Outcome

The natural history of patients with mild PS is usually benign. In the Second Natural History study, patients with catheter measured gradient less than or equal to 25 mm Hg had normal survival and no progression of their stenosis in 25 years of follow-up; patients with a gradient between 25 mm Hg and 49 mm Hg had a 20% chance of ever needing an intervention; and the majority of patients with a gradient more than or equal to 50 mm Hg experienced progressive stenosis and required intervention.



Figures 3A and B (A) Balloon dilatation of the pulmonary valve being performed with the balloon positioned across the annulus suggested by the waist (arrow); (B) Infundibular spasm (arrows) noted after the balloon dilatation, which may be responsible for transient persistence of gradient across the right ventricle to pulmonary artery

Infective endocarditis (IE) prophylaxis is not recommended for patients with PS. Patients with mild PS can live normal lives, without any exercise restriction. Those with moderate PS and normal biventricular function can participate in moderate levels of exercise and avoid competitive and static sports. In patients with severe PS, the stenosis must be resolved before they can resume unrestricted physical activity. While awaiting intervention, they should be restricted to low intensity sports.

SUBVALVAR PULMONARY STENOSIS

This may be secondary to either infundibular narrowing or due to anomalous muscle bundle in the RV cavity (double chambered right ventricle [DCRV]).

Primary infundibular stenosis Being rare, it accounts for about 5% of all cases of right ventricular outflow tract (RVOT) obstruction. It may be due to either an obstructive fibrous band at the junction of the main right ventricular cavity and the proximal infundibulum (resembling DCRV) or tunnel like narrowing of the infundibulum due to fibromuscular thickening of its wall. Hemodynamic and clinical features are similar to DCRV.

Double-chambered right ventricle Presence of anomalous muscle bundles across the mid-RV cavity divides it into a proximal high-pressure chamber and a distal low-pressure infundibular chamber. Embryologically, these muscle bundles could represent an arrested incorporation of the primitive bulbus cordis into the right ventricular body. A VSD is frequently present.

Clinical Features

Symptoms are similar to those with isolated valvar PS and progress with age. Symptoms of VSD may dominate if it is large. A loud pansystolic murmur usually with a thrill is audible located relatively low as compared to valvar PS (usually fourth left intercostal space). Click is absent and the pulmonary component of S_2 may not be as soft or delayed as in valvar PS. ECG may show evidence of RVH. An inverted T wave in lead V_{3R} may be the only finding in up to 40% patients with DCRV.

Diagnosis

Diagnosis as well as severity can be readily confirmed on echocardiography. Ventricular septum can also be evaluated for presence of VSD. Cardiac catheterization can reveal the presence of gradient from the high-pressure proximal inflow portion to the distal low-pressure infundibular portion. Magnetic resonance imaging (MRI) can be helpful in diagnosing as well as quantifying the severity in older children and adults with poor echocardiographic windows.

Management

It includes surgical excision of the anomalous muscle bundles in moderate to severe cases along with closure of any associated VSD. Long-term results after surgery are excellent.

PERIPHERAL PULMONARY STENOSIS

Stenosis of the pulmonary arteries, isolated or in association with other cardiac defects, accounts for 2–3% of all CHD. The stenosis may be single, involving the main pulmonary artery or either of its branches, or multiple, involving both the main and several smaller peripheral pulmonary artery branches.

Most common associations include valvar pulmonary stenosis, VSD, and tetralogy of Fallot. Several congenital syndromes are commonly associated with PPS namely congenital rubella, Williams, Noonan, Alagille, cutis laxa, Ehlers-Danlos syndrome, and Silver-Russell syndrome.

Embryogenesis

The proximal branch pulmonary arteries are embryological derivatives of the sixth branchial arches on either side. The peripheral portions of the pulmonary artery branches derive from the post-branchial pulmonary vascular plexus lying in close relationship to the growing lung buds. Embryologic basis of PPS tends to differ with the underlying insult. Teratogenic agents like rubella virus appear to interfere with normal formation of elastin tissues. Abnormal elastin production seems to be defect in Williams syndrome. Ductal closure may be etiology for proximal PA stenosis in cyanotic CHD.

Physiology

In cases with multiple bilateral stenoses, the RV and proximal PA pressure are elevated in proportion to the severity of stenosis. Resting RV pressure tends to remain normal in unilateral stenosis without vascular disease in the contralateral lung as a result of accommodation of the cardiac output by the normal contralateral pulmonary bed.

Clinical Features

Majority with mild to moderate stenosis tend to be asymptomatic. Those with severe multiple or bilateral stenosis may present with dyspnea on exertion, easy fatigability or signs of right heart failure. S_1 is normal and click is usually absent unless associated with valvar PS. S_2 is normally split with loud P_2 in cases with multiple peripheral stenosis. Characteristic murmur is systolic in nature beginning sometime after S_1 , heard well in pulmonary area and transmitted widely to axilla and back. Occasionally a continuous murmur may be heard signifying severe stenosis with presence of gradient even during diastole.

Investigations

Electrocardiogram

Typical findings include evidence of right atrial enlargement and RVH. Patients with Noonan and congenital rubella syndrome tend to have a higher incidence of left axis deviation.

Chest Radiograph

Right atrial and ventricular enlargement may be noted in those with severe PPS. Occasionally poststenotic dilatation of peripheral arteries may produce small vascular shadows in the perihilar lung fields.

Echocardiography

Elevated right ventricular pressure can be detected by Doppler interrogation of the tricuspid regurgitation jet. Proximal PA stenosis can be readily detected on color Doppler evaluation. However, distal PAs are difficult to assess by this modality.

Others

Alternative imaging such as computerized tomography (CT) and MRI are now considered the noninvasive modalities of choice for PPS. MRI and nuclear lung perfusion scans can quantify the proportion of blood flow to each lung segments which can aid in decision making regarding need and timing of intervention. Cardiac catheterization is now usually reserved for interventions.

Differential Diagnosis

These are similar to those with valvar PS. Presence of cyanosis should suggest diagnosis like tetralogy of Fallot or other complex cyanotic conditions.

Management

- **Surgery** Main PA and the proximal branch PA can be addressed surgically by enlarging the stenosed segment with autologous pericardial patch. Distal PAs are difficult to access surgically and are best treated by transcatheter measures.
- **Balloon angioplasty** Balloon dilatation affords relief by producing tear in the intimal and medial layer of the pulmonary vascular wall. Success rates have significantly improved with the availability of high-pressure balloons and cutting balloons. Initial success rate for isolated PPS is reported around 50% with a high restenosis rate of 35%. Resistant vessels may be dilated with cutting balloons with microsurgical blades mounted longitudinally on the balloon. Although initial success rate is reported as high as 92%, further long-term follow-up details are not available. Complications of angioplasty are seen in up to 10% cases and include pseudoaneurysm formation, hemoptysis, ipsilateral pulmonary edema, dissection, and thrombosis related to vascular access.
- **Intravascular stents** Excellent initial and mid-term follow-up results are reported with balloon angioplasty and placement of stainless steel balloon mounted stents with greatly enhanced success rate of 100% and increase in vessel diameter and more than 75% reduction in the pressure gradient. Stent redilatation may be needed especially in infants and young children. Complication (rate: 0–40%) includes stent migration, embolization, stent thrombosis, pulmonary edema and hemorrhage.

Infective endocarditis prophylaxis is not indicated for isolated PPS with intact ventricular septum. For those with surgically placed patch or catheter delivered stents, IE prophylaxis is indicated for the initial 6 months after procedure.

Outcome

Children with mild to moderate stenosis tend to remain stable. Patients with Williams, Rubella or Noonan syndrome may in fact have reduction of severity with age. Severe stenosis is progressive and if untreated, may lead to right ventricular failure or pulmonary hemorrhage from rupture of poststenotic aneurysmal artery.

IN A NUTSHELL

1. Pulmonary stenosis can be valvar, subvalvar or peripheral (involving the pulmonary artery).
2. Valvar PS constitutes 7% of all CHDs accounting for 80–90% of all lesions with right ventricular outflow tract (RVOT) obstruction.
3. Moderate and severe degree of stenosis is associated with right ventricular hypertrophy (RVH).
4. Majority of children with PS are diagnosed due to incidental detection of a murmur. Those with long standing moderate to severe stenosis present with exertional dyspnea and fatigue. Neonates with critical PS present with severe cyanosis at birth and may develop severe hypoxia and acidosis with PDA closure.
5. Balloon pulmonary valvuloplasty is the treatment of choice for moderate and severe PS.

MORE ON THIS TOPIC

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Chapter 40.18

Coarctation of Aorta

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Coarctation term derived from Latin *coartatio*, means crowding together. Aortic coarctation, therefore, indicates a narrowing at some point along the course of the aorta. Coarctation of aorta (CoA) varies considerably in its anatomy, physiology, clinical presentation, treatment options and outcomes.

EPIDEMIOLOGY

Aortic coarctation accounts for 7% of liveborn children with congenitally malformed hearts, with a higher incidence in stillborn infants. The overall incidence is 1 in 12,000, with a slight male preponderance with male : female ratio of 1.74 : 1.

ETIOLOGY

The exact etiology of coarctation is not known, but it is assumed to be multifactorial. It includes genetic predisposition, as it is known to recur in families. There is a suspicion of environmental influence with incidence of coarctation peaking in the late fall and winter. The genetic basis of occurrence of CoA has long been recognized, as it is an associated finding in 35% of Turner's syndrome. If one of the parents has CoA, the risk of recurrence in the offspring is about 2–4% and with a previous affected sibling with coarctation, the risk in next sibling is about 2%. There are various theories for development of coarctation:

Ductal tissue theory Normally the junction between the ductal tissue and elastic aorta is clearly defined and the ductal tissue into aortic wall does not extend beyond 30% of circumference (**Fig. 1**). However, in CoA, there is extensive infiltration of ductal tissue into aortic lumen, causing constriction of lumen resulting in obstruction.

Hemodynamic theory It proposes that coarctation develops because of hemodynamic disturbances that reduce the volume

of blood flow through the fetal aortic arch. In the normal fetus the aortic isthmus receives only 10% of the combined ventricular output explaining the observed lesser diameter of the normal isthmus (70–80% of that of neonatal ascending aorta). Intracardiac shunt lesions that diminish the volume of left ventricular (LV) outflow is said to promote development of coarctation in the fetus by reducing volume of blood flow through the aortic isthmus.

Neural crest cells Migration of neural crest cells towards the arch has been shown to play a role in development of interruption of the aortic arch. The same analogy can be applied to development of coarctation.

Fetal lymphatic obstruction This theory has been proposed for development of coarctation in patients with Turner's syndrome. It is suggested that fetal lymphatic obstruction, which may cause the webbed neck in Turner's syndrome, also leads to distended thoracic ducts that compress the fetal ascending aorta and thereby promote the development of coarctation.

PATHOPHYSIOLOGY

The terms used in the past such as *preductal* and *postductal* as well as *infantile* or *adult-type* CoA are misleading. CoA is almost always in a juxtaductal position. However, there are variations in morphology of coarctation with varying degree of obstruction (**Fig. 2**).

- **Shelf lesion** Typical coarctation lesion wherein there is an anterior and posterior shelf.
- **Waist lesion** It is a severe form of shelf lesion where the lumen constricts severely due to anterior and posterior shelf to form a tight waist with proximal tapering.
- **Tubular hypoplasia** Tubular hypoplasia is present when there is a uniform narrowing of part of the arch.
- **Arch atresia** A part of the arch is atretic with only fibrous cord connecting the atretic segment to distal aorta.
- **Interruption** This is an extreme form of arch obstruction in which a segment of the arch is absent. Depending upon the site of interruption, it is classified as Type A, B and C.

Pseudocoarctation refers to an anomaly characterized by buckling and kinking of aorta in vicinity of ligamentum arteriosum, resulting in elongation, tortuosity and distention of distal aortic arch and proximal descending aorta.

Simple versus Complex Coarctation

Simple coarctation Coarctation of aorta with or without patent ductus arteriosus (PDA).

Complex coarctation Coarctation of aorta associated with other intracardiac lesions such as bicuspid aortic valve (70–80%), ventricular septal defect (VSD) (35–40%), atrioventricular septal defect (AVSD) (10%), transposition of great arteries (TGA) (8%), double-outlet right ventricle (DORV) (6%). Other associations include hypoplastic left heart syndrome (HLHS), atrial septal defect (ASD), tricuspid atresia and pulmonary atresia with VSD.

Coarctation can also be a part of *Shone's complex* which includes left-sided obstructive lesions like supramitral membrane, parachute mitral valve, subaortic stenosis (membranous or muscular) and coarctation of the aorta. It can be extended to include other left side lesions like bicuspid aortic valve with stenosis and supra-ventricular stenosis. Extracardiac associated lesions include Berry aneurysm of circle of Willis (3–5%) and aberrant brachiocephalic artery anatomy (4–5%).

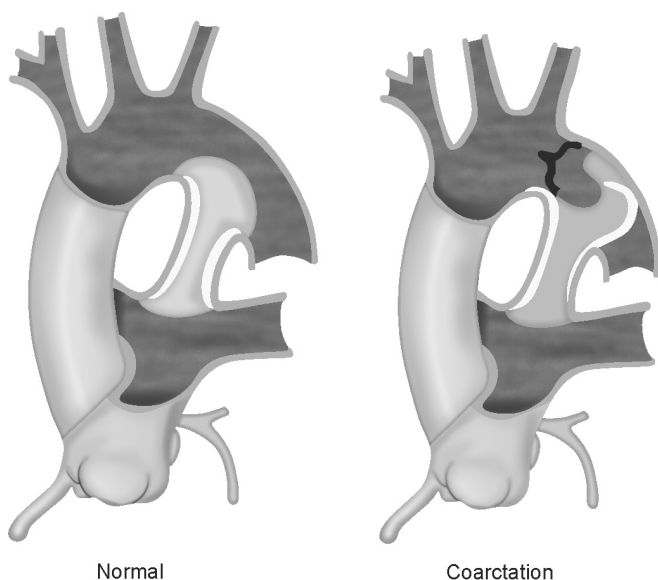


Figure 1 Extension of ductal tissue into the aorta: Normal: Less than 30% of circumference; CoA: Extensive infiltration around most of the aortic circumference

HEMODYNAMICS

Symptomatic newborn with CoA During fetal life (and at birth), the descending aorta is supplied mostly by right-to-left ductal flow

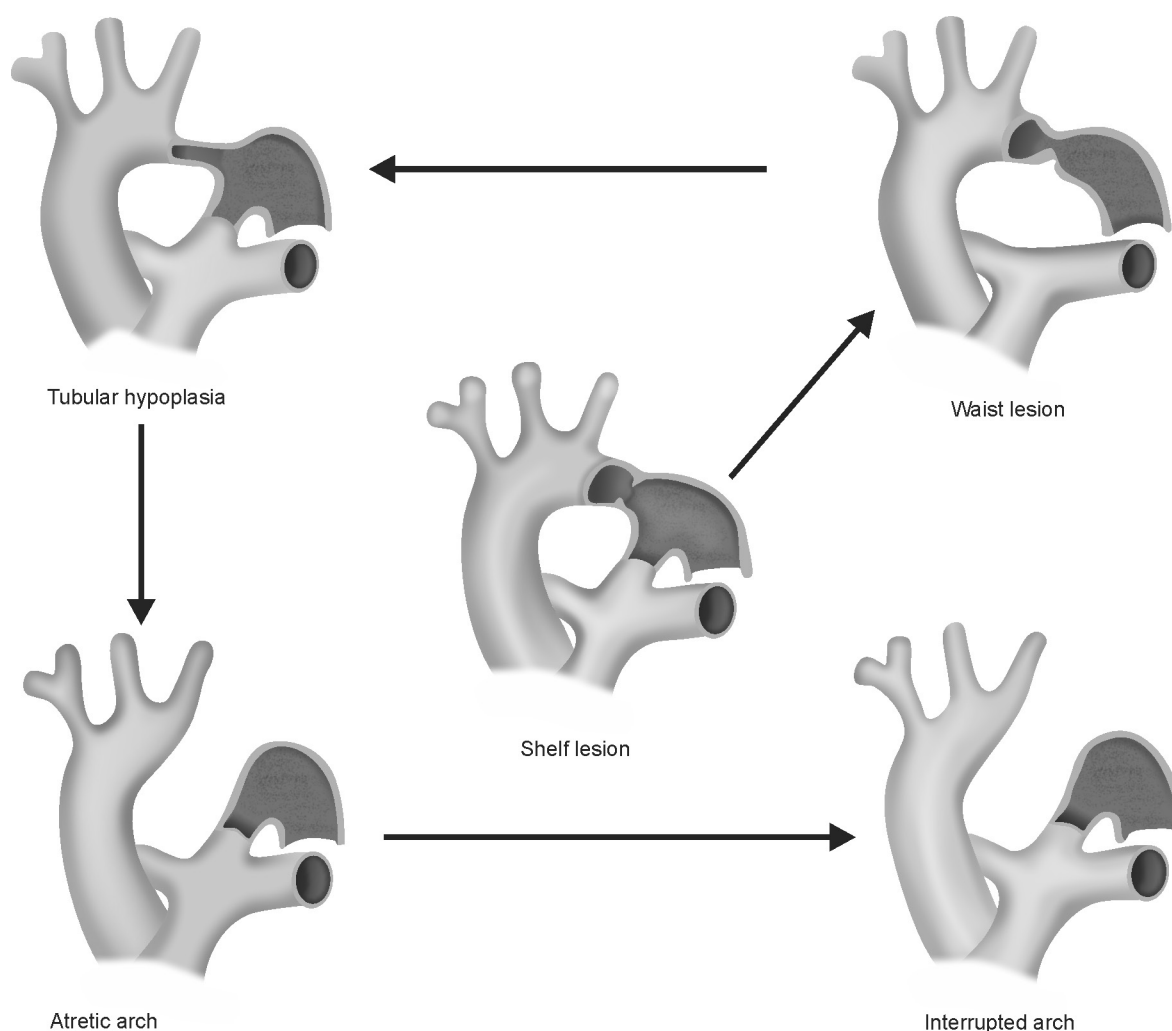


Figure 2 Variations in morphology of coarctation with varying degree of obstruction

and by a significantly reduced amount of antegrade aortic flow through the aortic isthmus. Other associated cardiac defects such as aortic arch hypoplasia, abnormal aortic valve, VSD, and mitral valve anomalies are often present. All these cardiac defects tend to decrease the antegrade aortic blood flow in utero. With ductal closure, a reduced antegrade aortic flow to the descending aorta produces symptoms early in life. Good collateral circulation has not developed in these neonates. Occasionally, infants without associated defects may become symptomatic because of LV failure, which results from a sudden pressure overload in early postnatal life.

Asymptomatic infants and children with CoA During fetal life, the descending aorta is supplied by both a normal amount of antegrade aortic flow through the aortic isthmus and normal ductal flow because associated cardiac defects are rare in these children. Good collateral circulation gradually develops between the proximal aorta and the distal aorta during fetal life.

Major *collateral circulations* between the aortic segments proximal and distal to the coarctation comprise of the internal mammary artery; arteries arising from the subclavian artery by way of the intercostal arteries and the anterior spinal artery.

CLINICAL FEATURES

Coarctation of aorta has bimodal presentation. Neonates and infants can present with acute LV failure or with cardiovascular

collapse, renal failure and acidosis. Children and adolescents may present with an incidental murmur, or as hypertension or any of the complications of hypertension.

Infancy Patients usually present with catastrophic features once the ductus closes. Most of the babies are associated with other intracardiac lesions. An infant with severe coarctation presents with acute heart failure, shock, and acidosis, which often develop suddenly at approximately 8–10 days of life. Multiorgan failure, particularly renal failure and/or necrotizing enterocolitis and death occur rapidly unless definitive medical and surgical interventions are provided immediately.

Children and adolescents Coarctation of the aorta often presents later in childhood as systolic hypertension or as a heart murmur. Some of them may present as complication related to hypertension, such as acute LV failure or stroke. Delayed diagnosis beyond infancy is common because the physical findings may be subtle and most of these children are asymptomatic. On careful investigation, some children will report lower-extremity claudication with exercise or frequent headaches.

Physical Examination

The appearance of a child with coarctation will vary depending on the mode of presentation. In an infant with congestive heart failure, one encounters a pale, irritable child in respiratory distress. Signs of congestive cardiac failure like tachycardia, dyspnea, diaphoresis

and hepatomegaly. In contrast, the appearance of an older child with coarctation may be entirely benign.

The hallmark physical findings in coarctation consist of discrepant arterial pulses and blood pressures in the upper and lower extremities. Arterial pulses below the coarctation are diminished in amplitude and delayed in timing compared with the proximal pulses (radiofemoral delay). Systolic blood pressure is elevated proximal to the coarctation, and a systolic pressure gradient is present between the arm and leg (difference more than 20 mm Hg).

In a sick infant the S_2 is single and loud; a loud S_3 gallop is usually present. No heart murmur is present in 50% of sick infants. Occasionally an ejection systolic murmur may be audible over the precordium arising from bicommissural aortic valve.

In an older child, a systolic thrill may be present in the suprasternal notch. The S_2 splits normally, and the A_2 is accentuated. An ejection click is frequently audible at the apex and/or at the base, which originates in the associated bicuspid aortic valve or from systemic hypertension. An ejection systolic murmur grade 2 to 4/6 is heard at the upper right sternal border and middle or lower left sternal border. A well-localized systolic murmur is also audible in the left interscapular area in the back.

Investigations

Chest X-ray The heart size may be normal or slightly enlarged if LV failure sets in. Dilation of the ascending aorta may be seen. An E-shaped indentation on the barium-filled esophagus or a 3-sign on overpenetrated films suggests CoA. Rib notching (**Figs 3A and B**) between the fourth and eighth ribs may be seen in older children but rarely in children younger than 5 years.

Electrocardiogram (ECG) Leftward QRS axis and left ventricular hypertrophy (LVH) are commonly found (**Fig. 4**). The ECG appears normal in 20% of patients.

Echocardiogram Two-dimensional echocardiogram (2D-ECHO) helps in establishing the diagnosis and gives information regarding site and extent of coarctation, presence of *posterior shelf* at site of coarctation, degree of isthmic and transverse arch hypoplasia, presence of LV hypertrophy and status of LV function.

Doppler evaluation Helps in quantifying the severity of CoA by assessing the gradients across the CoA segment. Poor pulsation of the abdominal aorta with continuous flow on Doppler is an indirect evidence of severe coarctation. It shows the gradient across the coarctation with continuous flow across the segment. This helps to assess the severity of coarctation.

Magnetic resonance imaging (MRI)/Computed tomography (CT) scan Echocardiography is a superior modality for the diagnosis of coronary heart disease (CHD) in infants and young children, and CT scan/MRI has a limited role in smaller children because of the need for sedation or anesthesia, transportation, use of contrast, radiation exposure and higher cost. However, CoA is an exception. CT and MRI offer better anatomical delineation of CoA.

Cardiac catheterization and angiography In most cases, sufficient information can be obtained from clinical and noninvasive examination to decide on an appropriate plan for management. Occasionally one may have to resort to CT/MRI. Cardiac catheterization is of limited value in the diagnosis of CoA. Its role is mainly for therapeutic interventions in the form of balloon angioplasty, with or without stenting.

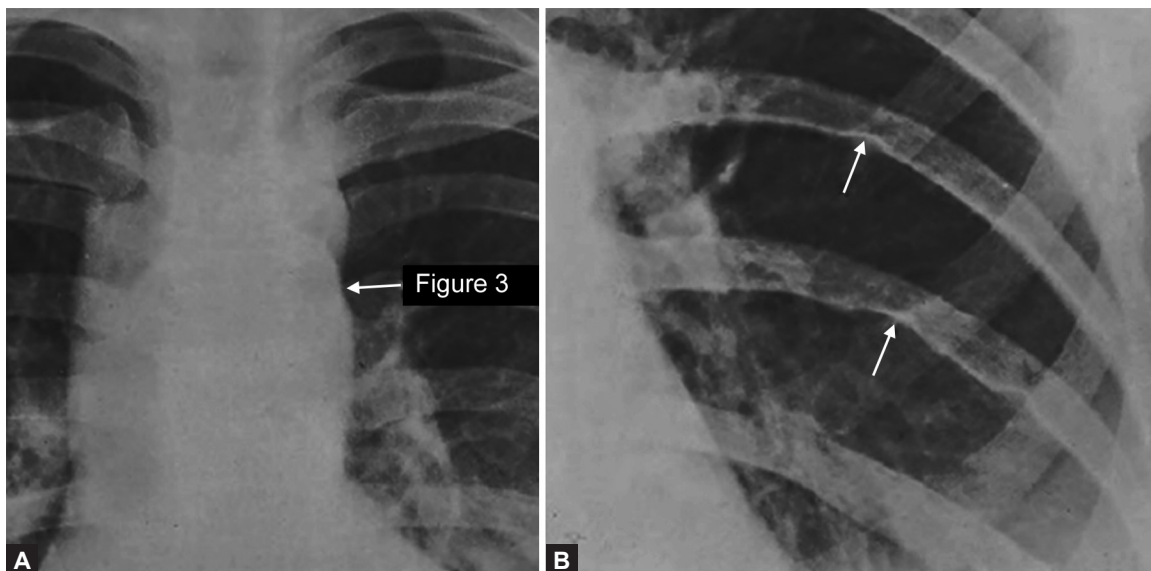
MANAGEMENT

Coarctation in a Newborn or Infant

Stabilization In symptomatic neonates, prostaglandin E1 (PGE1) infusion (0.05–0.1 mcg/kg/min) should be started to reopen the ductus arteriosus and establish flow to the descending aorta and the kidneys. Intensive anticongestive measures with inotropic agents (e.g., dopamine, dobutamine), diuretics and oxygen should be started.

Balloon angioplasty This can be a useful bridging procedure for sick neonates in whom standard surgical management carries a high risk. However, in well-compensated newborns and infants, balloon angioplasty is associated with a higher rate of recoarctation than surgical repair, and the rate of complications (including femoral artery injury) is also high during infancy.

Surgical intervention If CHF or circulatory shock develops early in life, surgery should be performed on an urgent basis (**Fig. 5**). A short period of medical treatment, as described earlier, improves the patient's condition before surgery.



Figures 3A and B Figure 3 sign (A), rib-notching (B)

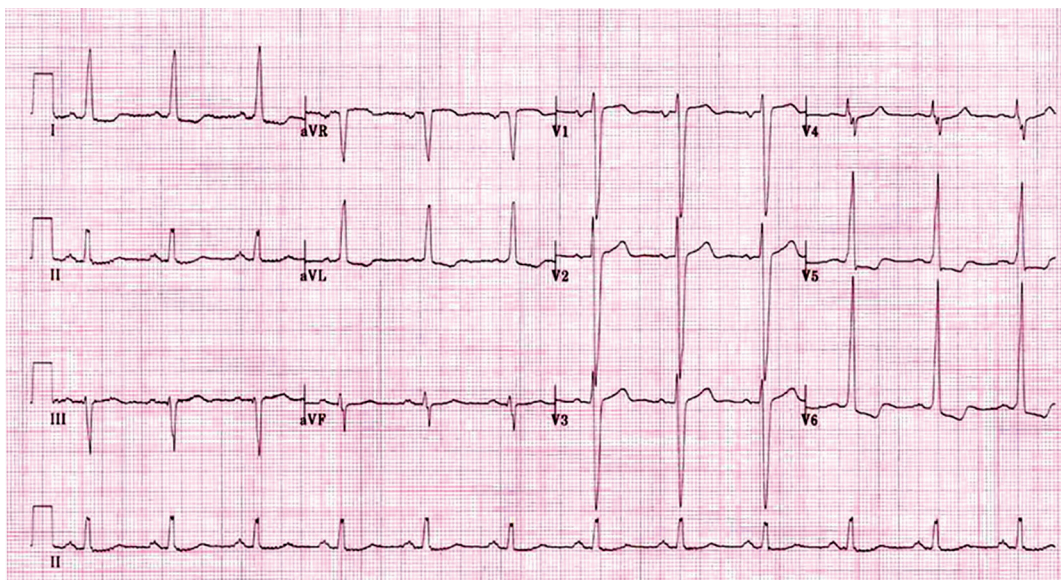


Figure 4 Left ventricular hypertrophy (LVH) with strain with left axis deviation (LAD)

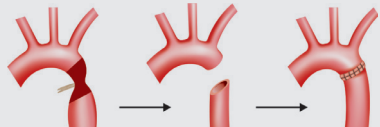
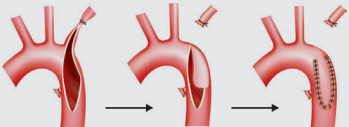
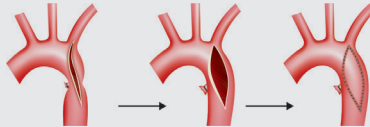
	<i>End-to-end anastomosis</i>	<i>Subclavian flap</i>	<i>Patch aortoplasty</i>
Indication	Discrete coarctation	Long-segment coarctation	Long-segment coarctation with hypoplastic transverse arch
Recurrence rate	< 10%	10–30%	Around 40%
			

Figure 5 Types of surgeries in coarctation of aorta

Coarctation in an Older Child

Medical management Children with mild CoA should be watched closely for hypertension in the arm. Drugs used for management of hypertension include beta-blockers, angiotensin converting enzyme inhibitors (ACEIs) and, angiotensin receptor blockers (ARBs). In children, on treatment with ACEI and ARBs, close monitoring of renal function is necessary. Good dental hygiene and precautions against subacute bacterial endocarditis (SBE) are important.

Balloon angioplasty For native unoperated coarctation, balloon angioplasty is now considered by most centers as primary treatment of coarctation (**Figs 6A to C**). It is also the procedure of choice for recoarctation. However, some centers still prefer a surgical approach. The most common acute complication of balloon angioplasty has been femoral artery injury and thrombosis, especially in small children. There is a possibility of aortic aneurysm formation with serious late complications. Also, hemodynamic results with deployment of stent are more predictable.

Balloon-expandable stent (covered/uncovered) Balloon expandable stent implanted concurrently with balloon angioplasty is now procedure of choice in western world in children older than 8–10 years old. This helps to reduce the chances of dissection and pseudoaneurysm formation.

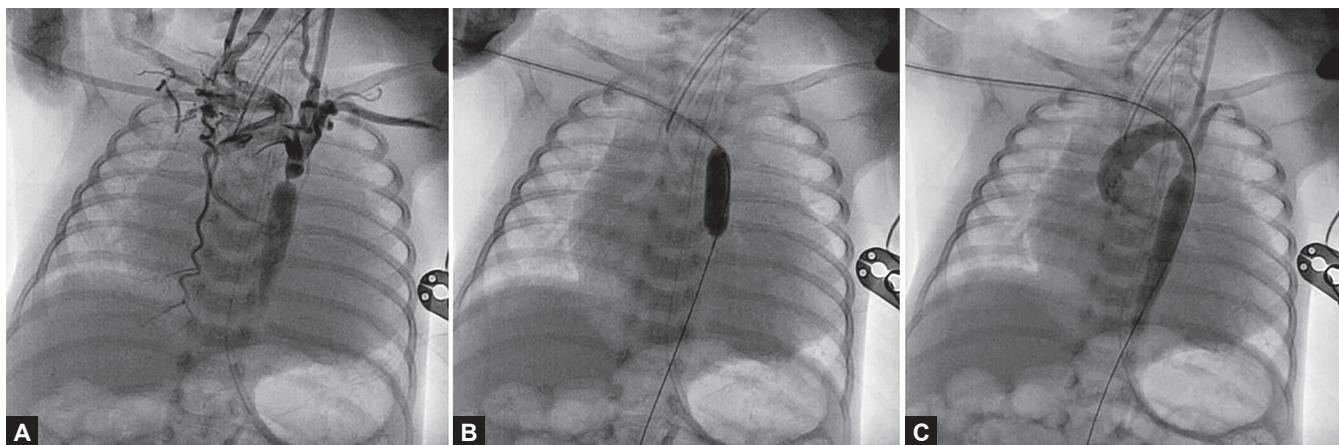
Surgical repair It includes end-to-end anastomosis, subclavian flap, patch aortoplasty and aortic jump graft. Elective correction is done between 2 years and 4 years in asymptomatic child with no hypertension and normal LV function. Earlier intervention is recommended in those with symptoms in form of shortness of breath, giddiness, black outs or development of hypertension or reduction of aortic diameter less than 50% or cardiomegaly on X-ray or LV dysfunction.

OUTCOMES

Surgical intervention in infants has mortality less than 2%. Complications include spinal cord ischemia, rebound hypertension and recoarctation (5%). Catheter intervention carries risk of mortality less than 3%.

Other complications include dissection, pseudoaneurysm, limb ischemia, recoarctation (10% in infancy, less than 5% in older children).

The prognosis for a normal life following successful repair of coarctation in childhood is excellent. Normal growth and development are to be expected, and no significant restrictions should be placed on physical activity. The long-term prognosis after coarctation repair may be profoundly affected by associated intracardiac lesions such as aortic or mitral valve disease. Patients who required repair of intracardiac defects in infancy, such as repair



Figures 6A to C Balloon dilation of coarctation of aorta: (A) Severe coarctation of aorta; (B) Balloon dilation; (C) Postdilation

of a VSD, may have long-term sequelae that include residual VSDs, postoperative heart block and progressive LV outflow obstruction. Such patients require lifelong cardiology follow-up, and many will require additional transcatheter or surgical interventions later in life.

MORE ON THIS TOPIC

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IN A NUTSHELL

1. Coarctation of aorta has bimodal presentation. Neonates and infants can present with acute LV failure or with cardiovascular collapse, renal failure and acidosis. Children and adolescents may present with an incidental murmur, or as hypertension or any of the complications of hypertension.
2. The hallmark physical findings in coarctation consist of discrepant arterial pulses and blood pressures in the upper and lower extremities. Arterial pulses below the coarctation are diminished in amplitude and delayed in timing compared with the proximal pulses (radiofemoral delay). Systolic blood pressure is elevated proximal to the coarctation, and a systolic pressure gradient is present between the arm and leg (difference more than 20 mm Hg).
3. Balloon angioplasty is now considered as primary treatment of coarctation.

Chapter 40.19

Aortic Stenosis

Smita Mishra

A normal aortic valve is a trileaflet structure, located at left ventriculoarterial junction. The term *aortic stenosis* (AS) is generally used to refer to any of the fixed left ventricular outflow tract (LVOT) obstructive lesions found at the level of aortic valve, above or below. At times obstruction of LVOT may be present at more than one level. The valvar aortic stenosis (VAS) is the most common, while subaortic and supravalvar AS are infrequent and they rarely manifest in early infancy. The supravalvar stenosis is usually suspected when child has certain dysmorphic facial features; whereas patients with subaortic stenosis may often have an associated operated or unoperated congenital heart disease.

ETIOLOGY

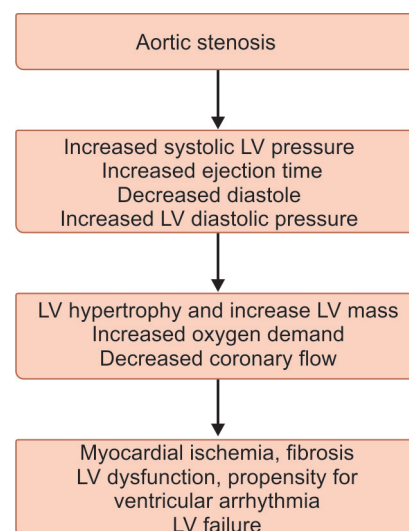
Valvar AS accounts for 70–91% of cases of AS. The majority of valvar AS in pediatric age group can be attributed to bicuspid valve. Few of them may present as critical AS in early neonatal period or later in infancy. Many of them may remain asymptomatic till the 4–5th decades of life. Unicuspid valves commonly present early as the critical AS and are poor candidate for ballooning procedures. The early stenosis of the tricuspid aortic valve can be due to the annular hypoplasia or myxoid dysplasia of valve leaflets. These anomalies are shown in **Figures 1A to E**.

The overall incidence of AS is 0.03–0.34 per 1,000 livebirths and constitutes about 7% of all congenital cardiac malformations. The prevalence of congenital bicuspid valve is 1.3%. Of that 2% patients will experience significant AS or regurgitation by adolescence.

PATHOPHYSIOLOGY

The AS increases work load of myocardium due to increased systolic pressure of LV and prolonged ejection time (**Flow chart 1**). Diastole-dependent coronary flow gets compromised. Moreover, the secondary LVH may be inappropriate and maladaptive and a substrate for malignant ventricular arrhythmias and heart failure. It is caused by the cusp deformities with or without narrowing of the *annulus*. It may manifest early infancy or later as the progressive obstruction of the inherently abnormal valve. The valvar AS has been found in isolation or may be an important component of familial syndromic states. *NOTCH 1* gene may be an etiological factor for familial occurrence of AS. It may be associated with genetic syndromes like Turner syndrome and Jacobsen syndrome.

Flow chart 1 Pathophysiology of aortic stenosis



Other Causes of Valvar AS

Usually mitral valve (MV) gets involved in rheumatic process and AS with or without aortic regurgitation (AR) is found additionally in one-fourth to one-fifth cases with rheumatic heart disease (RHD). Isolated aortic valve involvement is present in less than 10% cases. These patients are usually unsuitable for ballooning procedure. The systemic inflammatory diseases and metabolic disorders may also cause some degree of AS (**Table 1**).

VALVAR AORTIC STENOSIS

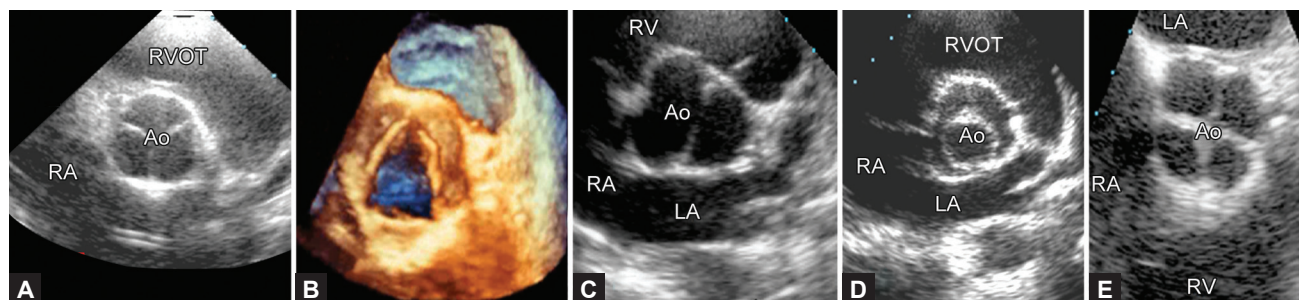
Table 2 provides differentiating features of various types of AS.

Aortic Stenosis Beyond Infancy

Normal growth and development is the rule in children presenting later in life. The common symptoms of easy fatigability, exertional dyspnea, angina pectoris, and syncope are present only in

Table 1 Causes of valvar aortic stenosis

Congenital	Abnormal number of cusps: Bicuspid, unicuspid, quadricuspid and other
Postinfective, autoimmune-collagen vascular	Rheumatic valve disease (late childhood mostly in adolescents), systemic lupus erythematosus, whipple disease
Metabolic	Fabry disease, Alkaptonuria, Type II hyperlipidemia, Marfan syndrome
Calcific or degenerative	



Figures 1A to E Numerical anomalies of aortic valve: (A and B) normal tricuspid aortic valve (Mercedes Benz sign), 3D image; (C) Bicuspid aortic valve (AV); (D) Unicuspid AV; (E) Quadricuspid AV.

Table 2 The comparison between various types of aortic stenosis (AS)

Features: Clinical and investigative	Valvar AS	Supra-valvar AS	Subaortic AS
Age of presentation	Any age	Usually after infancy	Usually after infancy
Sex	Male dominance		
Symptoms	CHF in neonates and infants, older kids effort intolerance, angina, syncope	Effort intolerance, angina, syncope	Effort intolerance, angina, syncope
Arterial pulse	Slow rise delayed peak narrow pulse pressure—pulsus parvus and tardus	Asymmetrical, right arm has high systolic pressure	Slow rise delayed peak, HOCM: brisk rise double peaked
Thrill location	Right and left upper sternal border radiating to carotids	Right upper sternal border	Right and left upper sternal border
Cardiac impulse	Heaving, localized, with presystolic motion, LV type, neonates may present with RV dominance	Heaving, localized	Heaving and localized
S ₁	Normal	Normal	Normal
S ₂	Normal or narrow or reverse split		
A ₂	Delayed		
P ₂	Normal		
LV S ₃	Frequently present		If present s/o severe AS with LV dysfunction
S ₄	LV-S ₄ may be present		
Ejection click	Constant ejection click right upper, left lower sternal border	No	
Murmur	ESM, crescendo-decrescendo, in right upper and left upper and lower sternal border and apex		ESM, crescendo-decrescendo, in RUSB, LLSB and apex
Murmur on standing	Decreased	-	Increased
Murmur on squatting	Increased		Decreased
Murmur on Amyl nitrite	Increased intensity		Increased intensity
ECG	LAD/LVH, Neonates/infants: RVH		LAD/LVH/abnormal Q wave may represent septal hypertrophy in a subset of patient
X-ray chest	Mild to moderate cardiomegaly, LVH, ascending Ao is dilated	Mild to moderate cardiomegaly, LVH, ascending Ao not dilated	
Associations	Turner syndrome, Jacobsen syndrome, <i>Notch1</i> gene	William syndrome	Other CHDs

moderate to severe stenosis. Easy fatigability is common in severe stenosis (15% in mild and 31% in severe AS), whereas angina or syncope are reported in less than 10% of patients even when peak-to-peak pressure gradients are greater than 80 mm Hg. Nevertheless, patients presenting with angina or syncope have grave prognosis.

Appearance of clinical signs other than murmur usually suggests moderate to severe stenosis. Arterial pulse in post neonatal infants is low amplitude and slow rising type (pulsus parvus et tardus) best appreciated in the carotid pulse. Beyond infancy, children with severe AS have forceful and sustained (heaving) LV apical impulse. Often, a thrill is felt in suprasternal notch (85% cases) and in precordium. A presystolic tap indicates forceful atrial contraction in response to elevated left ventricular end diastolic pressure (LVEDP). Auscultatory findings are described below:

Heart Sound

S₁ is normal. The splitting of the S₂ may be normal, narrow, absent or paradoxical due to delayed A₂, according to the severity of stenosis. Audible S₄, if present suggests severe aortic stenosis.

Systolic Constant Ejection Click

A hallmark of bicuspid AV remains same during the respiratory cycle in its timing and intensity even if the valve is functionally normal. Systolic ejection clicks occur in early systole and may result from either the abrupt opening of the semilunar valves or the rapid distention of the proximal aorta at the onset of ejection and they may disappear in presence of calcific AV. The aortic ejection click must be distinguished from tricuspid component (T1) of S₁ and S₄ and pulmonary ejection clicks.

Ejection Systolic Murmur

The systolic (diamond-shaped on phonocardiographic recording) crescendo-decrescendo ejection murmur follows the click, is heard over the right upper sternal border (primary aortic area), lower sternal border and/or apex (**Fig. 2**). It radiates into the neck over the carotid arteries bilaterally. Increasing severity of stenosis is accompanied by a louder, harsher, and later-peaking ESM.

Presence of hyperdynamic systolic carotid thrill, pulsus bisferiens and early diastolic murmur suggests associated AR.

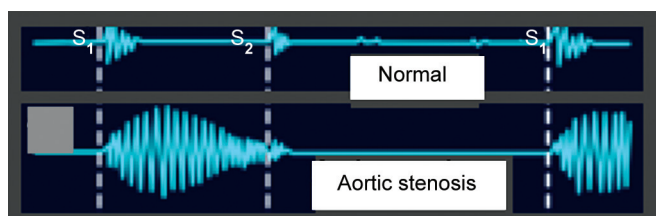


Figure 2 Phonocardiogram: Murmur of aortic stenosis

Aortic Stenosis in Neonates

Any neonate presenting with circulatory shock and low volume pulses must be immediately investigated for critical left sided obstructive cardiac lesions. Neonates with critical AS are often moribund and have congestive heart failure as well as circulatory shock. They often get wrongly interpreted to have right heart failure due to presence of epigastric pulsations and hepatomegaly. Critical AS is categorized as a ductus dependent CHD because these neonates can be saved and temporarily palliated till corrective surgery with prostaglandin E_1 infusion. The outcome may be potentially lethal if LV shows the complex myocardial changes and hypoplasia.

Investigations

Electrocardiograph

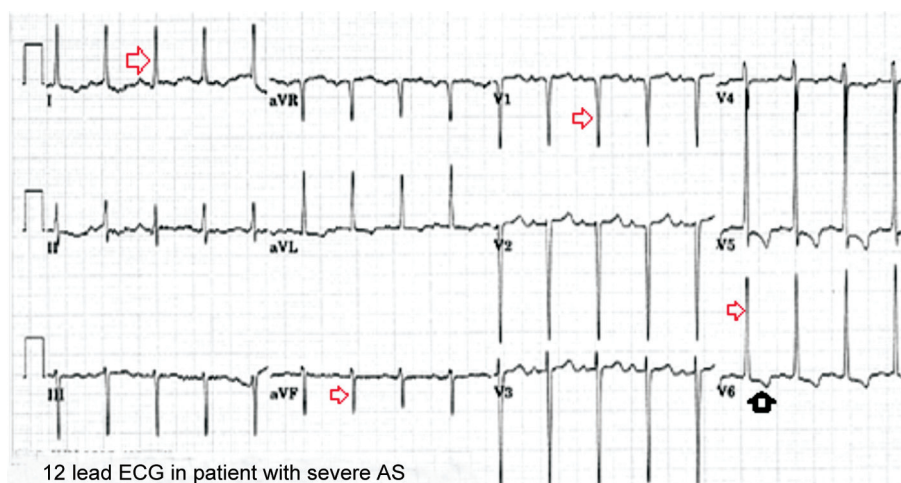
The ECG in AS has a low sensitivity and may be normal in a case with severe AS. In older infants and children, the resting ECG must be evaluated for age specific voltage criteria of left ventricular hypertrophy (LVH). The Holter monitoring of these patients may help in recognizing the dysrhythmias. The presence of arrhythmias predisposes for sudden cardiac death (SCD).

P wave is normal or bifid suggesting presence of mitral regurgitation. The QRS axis may be normal. The depolarization loop is clockwise with q waves seen in inferior leads— aVF III. LVH is represented by tall R wave in lead II, aVF , deep S in V_1 , tall R waves in V_{5-6} , and deeply inverted T waves also seen pointing against the QRS complex, so called wide QRS-T angle (**Fig. 3**).

In neonates and infants, there may be significant RVH and normal left ventricular forces. In infants having hypoplastic LV, R wave in left leads will be smaller. Increased left ventricular forces are not seen in neonatal period.

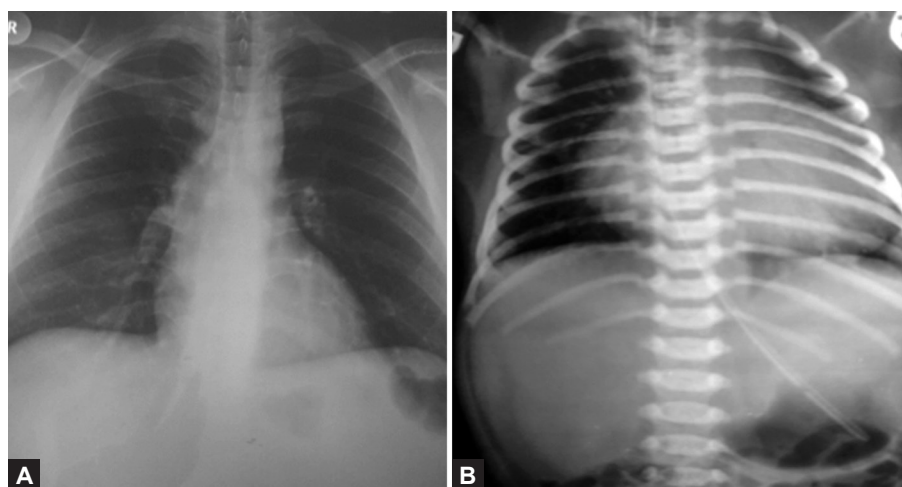
Radiology

Frontal projection of X-ray chest shows normal or minimally enlarged heart shadow in moderate to severe AS (**Figs 4A and B**).



12 lead ECG in patient with severe AS

Figure 3 ECG in severe aortic stenosis: Left ventricular hypertrophy (LVH) is represented by tall R wave in lead II and aVF , deep S in V_1 , tall R waves in V_{5-6} , deeply inverted T waves also seen pointing against the QRS complex, so called wide QRS-T angle. (Q wave changes are not seen in inferior leads)



Figures 4A and B Chest X-ray in aortic stenosis. (A) Dilated aorta in a 15-year-old patient with bicuspid aortic valve AS/AR; (B) X-Ray chest of a 4-day-old neonate with critical AS cardiomegaly and hepatomegaly. Pulmonary venous hypertension (PVH) cannot be appreciated in this over-exposed bedside film

Table 3 summarizes the findings associated with various levels of left ventricular outflow tract obstruction (LVOTO).

Echocardiography

Echocardiography in multiple views evaluates the LVOT and aortic root, the hemodynamic effect of AS, as well as presence and absence of associated lesions. Two-dimensional assessment (2-D mode) of aortic root is done at 4 levels: the annulus, the sinuses of Valsalva, sinotubular junction and the proximal ascending aorta. The parasternal long axis view is the best view to measure the aortic valve annulus and aortic root. Ascending aorta and arch can be measured in suprasternal long axis view. The valve morphology is best evaluated in 2D or 3D short axis parasternal view. Ascending aorta is evaluated in right high parasternal view and arch and descending aorta can be seen in suprasternal views. The major aortic abnormalities like progressive dilatation of aortic root, coarctation of aorta, dissection of aorta or carotid arteries must be looked for.

Doppler Echocardiography

Normally, blood flow across the aortic valve is laminar and peak systolic velocity of blood flow across the valve rarely exceeds 1.5 m/s. An aortic jet velocity greater than 4.0 m/s, Doppler gradient more than 40 mm Hg and aortic valve area less than 0.5 cm² suggests severe AS. The catheter derived peak-to-peak gradient is best corresponds with mean Doppler gradient and is the gold standard. The diastolic function of LV is assessed by MV inflow velocity graph and tissue Doppler assessment of mitral valve annular velocities.

Catheterization, CT and MRI

Diagnostic catheterization is rarely done; therapeutic catheterization is resorted to in appropriate cases. CT/MRI is done when aortic evaluation is required.

Role of Exercise Testing

Exercise testing can identify the limited exercise capacity and reveal symptoms in many (usually one-third) apparently asymptomatic children and adolescents. The one year prognosis of patients with a normal exercise test is excellent. In contrast, a positive exercise

test predicts the onset of a cardiac event in a sizeable proportion of patients. The advice for athletic activities can be made based on exercise testing.

Management

Medical Management

The decongestive management is needed for patients presenting with the left ventricular failure. The neonate presenting early may get benefit from prostaglandin infusion.

Balloon Dilatation

The balloon dilatation of aortic valve (BAV) or balloon aortic valvoplasty, first reported by Lababdi et al in 1984, is the safest and efficient method particularly for small infants who have limited options in absence of ideal size of prosthesis (**Figs 5A to C**). The balloon size used should not exceed the aortic annular size. The criteria for successful BAV result are: fall in gradient more than 50% of predilatation values, improved LV function and no more than minimal AR. The procedural success has been reported to be from 88 to 96%. The reported actuarial intervention-free rate after the 12 years is 60%. Optimal timing of ballooning is summarized in **Table 4**.

Surgical Interventions

The surgical options for infants and growing children, namely, open aortic commissurotomy, Ross procedure (**Fig. 6**) or valve replacement, are limited. AV replacement is usually management of choice in absence of a successful repair technique. The mechanical prosthetic replacement has shown acceptable long-term results but needs lifelong anticoagulation. Use of bioprosthetic valve (BPV) or tissue valves, homograft or heterograft, avoids the need for anticoagulation but less durability of prosthesis and chances of early reinterventions, are unresolved issues related to their use. The immediate results of Ross commissurotomy are good. The reported postoperative mortality is 5–20%. About 75% of tissue valves may need reintervention. The reoperation rate for mechanical prosthetic replacement is 55–90% on 15 years follow-up. Though BAV is the first line of management for the neonatal AS, modified Norwood operation may be the only treatment strategy for neonate with critical AS and concomitant LV hypoplasia.

Outcome

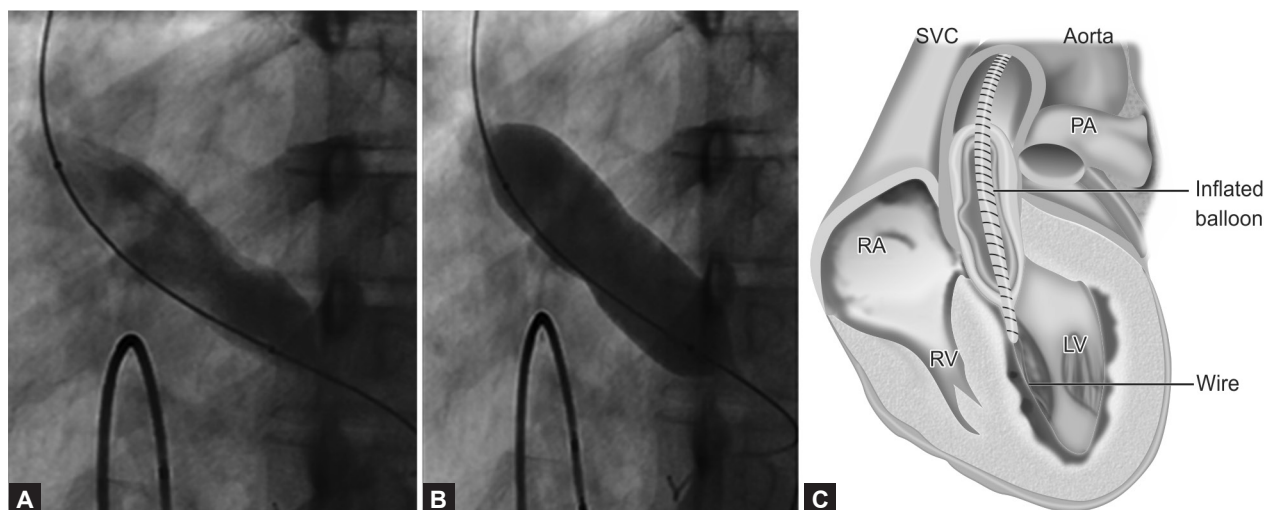
The outcome of bicuspid aortic valve depends on evolution of stenosis/regurgitation, aortic root dilatation and onset of infective endocarditis (IE). Infants with AS presenting early have more severe stenosis and higher mortality with or without treatment. But, beyond infancy, the mean age of death due to AS is 35 years. Cause of death is usually sudden cardiac death (SCD) in about 50% cases. The progressive LV dysfunction and congestive heart failure (CHF) is the cause of death in other 50% cases. AS is a progressive disease and patient with mild obstruction may also show increment in gradient later in life. The dilatation of aortic root beyond 45 mm makes it vulnerable for aortic dissection or rupture. The risk of IE associated with diseased aortic valve is more prevalent in young male and in patients with severe AS.

SUPRAVALVAR AORTIC STENOSIS

Supravalvar aortic stenosis (SVAS), a rare cause of AS, manifests as focal or diffuse narrowing of sinotubular junction and the ascending aorta. SVAS is often associated with Williams syndrome. Williams-Beuren syndrome with associated SVAS is known to be

Table 3 Summary and interpretation of radiological findings in aortic stenosis

Classical findings (All types of AS)	Frontal X-ray chest—normal or minimally enlarged heart shadow in moderate to severe AS; cardiac apex—rounded apex, displaced left and down in PA view, posterior displacement of cardiac shadow is seen in left lateral view
Enlarge RA, RV dominance	In neonates in critical AS (+/- hypoplastic LV, TR, MR)
Enlarged LA	LV dysfunction, associated PDA. Mitral regurgitation
Pulmonary venous hypertension	Critical AS; classical pulmonary edema in severe AS and LV failure
Dilated aorta	Valvar AS usually with bicuspid valve with or without AR
Inconspicuous ascending aorta	Associated supravalvar AS, infants and small children
Calcified valve	Elderly patients with AS
Evidence of operated or unoperated CHD	Subvalvar AS



Figures 5A to C Balloon aortic valvoplasty. (A) Partially inflated balloon; (B) Inflated balloon with waist remaining; (C) Balloon placement

Table 4 Valvar aortic stenosis: Timing of intervention

For infants and older children
<ul style="list-style-type: none"> • Left ventricular dysfunction: Immediate intervention by balloon dilatation, irrespective of gradients (Class I) • Normal left ventricular function: Balloon dilatation if any of these present: (i) gradient > 80 mm Hg peak and 50 mm Hg mean by echo-Doppler (Class I); (ii) ST-T changes in ECG with peak gradient of > 50 mm Hg (Class I); (iii) symptoms due to AS with peak gradient of > 50 mm Hg (Class IIa). In case of doubt about severity/symptoms, an exercise test may be done for older children (Class IIb)
For neonates
Balloon dilatation if symptomatic or there is evidence of left ventricular dysfunction/mild left ventricular hypoplasia (Class I), or if Doppler gradient (peak) > 75 mm Hg (Class IIa)

due to microdeletion in the elastin gene located at chromosome 7q11.23, inherited as an autosomal dominant disorder with variable penetrance in families.

Pathophysiology

Supravalvar aortic stenosis has three forms (1). The most common classical hour glass type presenting with focal narrowing of STJ and proximal aorta; (2) Membranous diaphragm at STJ but no narrowing outside; (3) Diffuse variety involving ascending aorta, arch vessels and may be associated with coarctation of aorta. The usual pathological changes are seen in media and intima. There may be smooth muscle hypertrophy, abnormal elastic fibers or varying degree of collagenization of media. It may also involve AV and coronary ostium and may present with ostial stenosis or dilatation of coronary artery. Stenosis of peripheral arteries like renal and mesenteric artery may be seen in 30% cases.

The resistive aortic flow and systolic hypertension of ventricle is common physiological effect of SVAS. There might be associated valvar AS and bicuspid AV in about 50% cases and subvalvar stenosis in about 16% cases.

Clinical Features

The special dysmorphic features of Williams syndrome associated with SVAS are small upturned nose, long philtrum, wide mouth, full

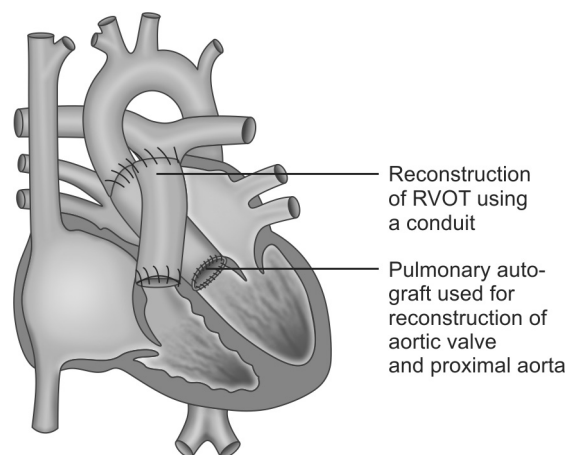


Figure 6 Ross procedure: excision of diseased aortic valve and placement of pulmonary autograft (blue). A valved conduit is placed to reconstruct right ventricular outflow tract (RVOT)

lips (**Fig. 3**). Mostly, there is the marked increase in the pressure of pulse of right upper limb (asymmetrical pulse in upper limb), an important clue to clinical diagnosis. This is known as *Coanda effect* and happens due to preferential flow of blood towards right upper limb. The precordial findings are almost similar to valvar AS (**Table 2**). Additionally, there might be bruit over peripheral arteries suggesting stenosis of the arteries. Children with coronary ostial stenosis may present with typical angina. It is difficult to differentiate level of LVOT obstruction on the basis of ECG or X-ray chest (**Table 3**). However, dilated aorta seen in X-ray chest of the patient with valvar AS is almost never seen in patients with SVAS (**Fig. 4**).

Treatment

Essentially, treatment of SVAS is surgery in symptomatic patients who have mean LVOT gradient 50 mm Hg or above.

SUBVALVAR AORTIC STENOSIS

Subvalvar aortic stenosis (SAS) is usually a progressive anatomical obstruction leading to the fixed LVOTO. SAS often has a dynamic component contributing to the obstruction.

It usually is an acquired lesion rarely presenting during early childhood. The abnormal flow pattern of blood has been credited for SAS in these patients. Common associations (present in 20–25% cases) are ventricular septal defect, atrioventricular septal defect, patent ductus arteriosus and bicuspid aortic valve, Shone complex, interrupted aortic arch and persistent left superior vena cava.

Diagnosis

The precordial findings, ECG, and X-ray chest are described in **Table 3**. The 2D, 3D transthoracic or transesophageal echocardiography with color and spectral Doppler are diagnostic; it evaluates its anatomical and functional aspects as well as the role of dynamic component. Additional information may be obtained by CT angiography and MRI.

Treatment

Medical Management

The β -blockers and calcium channel blockers help in reducing the contractility and hence they reduce dynamic component of the obstruction. Also, maintaining good hydration is important.

Surgery

Surgery is the treatment of choice for significant SAS. For hypertrophic cardiomyopathy, septal ablation is an alternative treatment. There are various surgical methods according to the type of SAS. Mitral valve replacement or repair may be needed in selected group of patients.

Shone's Complex

Described by Shone et al, in 1963, this complex is a constellation of left sided obstructive lesions which includes (1) Parachute MV; (2) Supra mitral ring; (3) Subaortic stenosis; and (4) Coarctation of aorta. The clinical presentation varies according to the severity of lesions. Therefore, management has to be customized and overall outcome cannot be predicted. The clinical deterioration of babies due to CHF and circulatory failure is common in first few weeks of life. Those infants presenting with severe LVOTO have high mortality, morbidity, and high rate of reinterventions.

IN A NUTSHELL

1. Aortic Stenosis refers to a fixed left ventricular outflow tract obstructive lesion at the level of aortic valve (valvar AS), above (supravalvar AS) or below (subvalvar AS). At times obstruction of left ventricular outflow tract may be present at more than one level.
2. Aortic stenosis can present in neonatal period, remain asymptomatic, or present anytime in childhood.
3. In older children, exertional dyspnea, angina pectoris, and syncope are the characteristic features in moderate to severe stenosis.
4. The aortic valvar stenosis is the most common, while subaortic and supravalvar aortic stenosis are infrequent and they rarely manifest in early infancy. Balloon valvuloplasty is the treatment of choice with excellent outcome.
5. The supravalvar stenosis is usually suspected when child has certain dysmorphic facial features suggestive of William syndrome. Long-term outcome of the isolated, nonsyndromic focal SVAS are more or less excellent.

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Chapter 40.20

Clinical Approach to Infants and Children with Cyanotic Congenital Heart Disease

M Zulfikar Ahamed

Recognizable cyanosis is due to a reduced hemoglobin (Hb) content of more than 4–6 g/dL in capillary blood. With a normal or high Hb content, desaturation will produce a significant amount of reduced Hb to cause cyanosis, while in severely anemic infant, even in the presence of desaturation; reduced Hb will not reach the value to cause clinical cyanosis.

Recognizing central cyanosis in an infant, especially a neonate is quite tricky. Ambient light, wall paint, skin color and examiner's experience are some of the factors determining accurate detection of cyanosis. In a fair-skinned child, saturation below 85% is required to produce clinical cyanosis. If any baby is really blue, its saturation will be usually around 70%.

Situation	Saturation
Arterial desaturation	< 95%
Hypoxemia	< 90%
Clinical cyanosis	< 85%

CENTRAL CYANOSIS: A CLUE TO CONGENITAL HEART DISEASE

Central cyanosis in a heart disease is due to a right to left shunting either intracardiac or extracardiac. To put it in a different way, congenital cyanotic heart diseases are anomalies in which some systemic venous return will inevitably reach the systemic circulation without passing through lung. There are however many potential pitfalls in clinical recognition of congenital cyanotic heart disease.

- Clinical assessment of cyanosis can be inaccurate depending on hemoglobin status.
- Congenital cyanotic heart disease with increased pulmonary blood flow due to admixture physiology can have saturations varying from 85% to 90% so that there is no clinically evident cyanosis.
- Some acyanotic congenital heart disease (CHD), especially large left to right shunts can develop severe chest infection and CHF and cause central cyanosis.
- Primary lung conditions sometimes can mimic cyanotic heart disease.

Cyanosis in a cyanotic CHD is often uniform and constant. Occasionally, differential cyanosis can occur—upper limbs are pink and lower limbs are blue or alternatively, upper limbs blue and lower limbs pink. Clinical differential cyanosis requires at least a difference of 10% saturation between upper limbs and lower limbs. Causes are listed in **Table 1**.

CONGENITAL CYANOTIC HEART DISEASE IN INFANCY AND CHILDHOOD

Majority of infants and children with congenital cyanotic heart disease (CCHD) present with history of cyanosis—on crying or at rest. A few infants present for the first time with cyanotic spells. Occasionally, a child with CCHD will present with a cerebrovascular accident or brain abscess.

Table 1 Causes of differential and differential reversed cyanosis

Differential cyanosis	
Pink upper limbs and blue lower limbs	<ul style="list-style-type: none"> • Patent ductus arteriosus (PDA) with Eisenmenger syndrome • Persistent pulmonary hypertension (PPHN) in neonate • Hypoplastic left heart syndrome (HLHS) • Interrupted aortic arch syndrome (IAAS)
Reversed differential cyanosis	
Blue upper limbs and pink lower limbs	<ul style="list-style-type: none"> • Transposition of great arteries (TGA) with PDA with/without CoA

Note: PDA with Eisenmenger syndrome need not have differential cyanosis if it has associated atrial septal defect (ASD) or ventricular septal defect (VSD).

Cyanotic children may be classified into those who have decreased pulmonary blood flow (\downarrow PBF) or those with increased pulmonary blood flow (\uparrow PBF). CCHD with reduced PBF can be further categorized into two major groups: (a) With pulmonic stenosis; and (b) With pulmonary hypertension. Both effectively reduce blood flow across lungs and cause central cyanosis. There is a right to left intracardiac shunt at some level. Some infants with secondary pulmonary hypertension may have initial history suggestive of increased PBF.

Pulmonic stenosis most often occurs in association with ventricular septal defect (VSD). Majority of children with CCHD with reduced PBF have an interventricular communication and some degree of pulmonary stenosis (PS). Tetralogy of Fallot (TOF) is the prototype of this group. In some, PS is associated with intact IVS (inter ventricular septum) and right to left shunt occurs through a small atrial septal defect (ASD) or patent foramen ovale (PFO).

GROUP I CCHD

Decreased Pulmonary Blood Flow; PS with VSD

The common lesions in Group I are:

1. Tetralogy of Fallot (TOF)
2. Pulmonary atresia with VSD
3. Tricuspid atresia
4. Double outlet RV (DORV). VSD. PS
5. L-TGA. VSD. PS (Corrected TGA)
6. D-TGA. VSD. PS
7. AV septal defect with PS
8. Single ventricle with PS
9. Truncus arteriosus with PS.

Almost all of them share clinical features (**Table 2**) like deep central cyanosis, absent features of congestive heart failure (CHF), normal or near normal cardiac size, single S2 and an outflow murmur. Some may have some deviation from the set pattern, which may help in reaching a more specific diagnosis. Electrocardiography will be variable and is of greater use in differentiating between individual CHD among this group. Salient clinical features of individual conditions in Group I (CCHD; \downarrow PBF; PS with VSD) are outlined below:

Pulmonary atresia with VSD There is no outflow murmur; instead children will have a high volume pulse, a murmur of either patent ductus arteriosus (PDA) or main aorto pulmonary collateral arteries (MAPCA) or occasionally an ejection click due to dilated aorta.

Table 2 Characteristics of Group I CCHD with ↓PBF; PS with VSD

Characteristic history	Physical findings
Progressive central cyanosis from infancy resulting in deep cyanosis	No signs of CHF; JVP is usually not elevated
Hypercyanotic spells in infancy	No cardiomegaly
Squatting in childhood	Quiet precordium devoid of left parasternal heave or hyperkinetic impulses
No recurring chest infections	Single S ₂ (Second sound)
No history suggestive of CHF	An outflow systolic murmur of varying intensity
Progressive central cyanosis from infancy resulting in deep cyanosis	
Hypercyanotic spells in infancy	
<i>Chest X-ray</i>	
Normal cardiothoracic ratio, pulmonary oligemia, small sized pulmonary arteries, right-sided aortic arch (sometimes); 25–30% in TOF and in PA with VSD.	
<i>Electrocardiography</i>	Variable (Refer Table 3)

Abbreviations: CCHD, congenital cyanotic heart disease; PBF, pulmonary blood flow; PS, pulmonary stenosis; VSD, ventricular septal defect; CHF, congestive heart failure; JVP, jugular venous pressure; TOF, tetralogy of Fallot.

Tricuspid atresia will have a very early presentation with deep cyanosis, absent right ventricular impulses, prominent 'a' wave in jugular venous pressure (JVP) and sometimes a left ventricular apical impulse.

DORV. VSD. PS Clinically indistinguishable from TOF.

L-TGA. VSD. PS More often associated with dextrocardia; shares all the clinical features of TOF but for a very loud single S₂ at pulmonary area due to a L-posed anterior aorta. There could be an apical murmur-MR like, due to left AV valve (Tricuspid) regurgitation.

D-TGA. VSD. PS will have intense, early onset cyanosis from newborn days onwards and outflow murmur. There could be mild cardiomegaly.

AV septal defect with PS can have an LV impulse, an apical murmur due to left AV valve regurgitation (Mitral) in addition to RVOT murmur and a S₃.

Single ventricle with PS will be almost be like TOF; there could be an LV apical impulse, mild cardiomegaly and a long systolic murmur in spite of significant cyanosis.

Chest X-ray

Both TOF and PA with VSD will have right aortic arch in 25–30% of cases; Tricuspid atresia will have no upturned apex but will have prominent right atrium. L-TGA will have an L-posed aorta forming upper part of cardiac border. D-TGA will have prominent right atrial enlargement (RAE).

ECG

Findings include RAD, and RVH without strain. TOF will have early transition in precordial leads. RAE is not a feature in this group. The individual lesions will have certain characteristic ECG abnormalities (Table 3).

GROUP II CCHD

Severe PS; Intact Interventricular Septum (IVS)

Severe valvar PS in the long run can progress and cause raised filling pressures in right ventricle, which is transmitted to right atrium. If there is a PFO or ASD, right to left shunt occurs through it and causes central cyanosis later. Right ventricle dilates and develops dysfunction causing considerable cardiac enlargement. The clinical presentation is unique among CCHD with decreased PBF.

These children will have central cyanosis, elevated JVP with prominent a wave and v waves, cardiomegaly, hyperdynamic precordium, significant parasternal heave, single S₂ or wide split with delayed soft P₂, and S₃. Murmurs occur due to tricuspid regurgitation (TR) and PS. TR murmur may be more prominent!

ECG will show severe RVH with strain pattern. This is in contrast to TOF situation where there is no RV strain pattern as RV is used to systemic pressures from outset. RV pressure in this group can be suprasystemic causing a qR in V1 or V3 R. RV strain is evident with ST – T changes in V1-V6.

GROUP III CCHD

Decreased PBF with Pulmonary Artery Hypertension (PAH)

Just as PS causes impedance to right ventricular blood flow to lungs, severe PAH due to pulmonary vascular occlusive disease (PVOD)

Table 3 ECG findings in CCHD with decreased pulmonary blood flow (PBF); VSD with PS

	P wave	PR	QRS axis	RVH	LVH	BVH
TOF	N	N	RAD	++	—	—
PA/VSD	N	N	RAD	++	—	—
TA	RAE	N	LAD	0	++	
DORV	N	Prolonged	RAD-extreme	++	—	+
L-TGA	N	Prolonged	LAD	++	—	—
D-TGA	RAE	N	LAD	++	—	—
AVSD	RAE	Prolonged	LAD	±	—	+
Single ventricle	N	N	LAD ?	±	—	+
Truncus	N	N	RAD	+	—	+

Abbreviations: CCHD, congenital cyanotic heart disease; PBF, pulmonary blood flow; PS, pulmonary stenosis; VSD, ventricular septal defect; TOF, tetralogy of Fallot; D-TGA, D-transposition of great arteries; PS, pulmonary stenosis; DORV, double outlet RV; RAD, right axis deviation; LAD, left axis deviation; RVH, right ventricular hypertrophy; LVH, left ventricular hypertrophy; RAE, right atrial enlargement.

will cause considerable impedance to blood flow to lungs causing reduced pulmonary flow. A communication between chambers at any level will set up a right to left shunt causing central cyanosis. The classical condition, Eisenmenger syndrome, which is defined as a condition in which a left to right shunt develops severe PVOD so that bidirectional or right to left shunt occur causing central cyanosis.

Eisenmenger reaction can occur in ASD, VSD, PDA and AP window. Except ASD all Eisenmenger conditions behave similarly clinically. They will start as significant left to right shunt in infancy and develop cyanosis in the 2nd or 3rd decade, will have mild to moderate cyanosis, minimal or no cardiomegaly, no CHF and clinical findings of severe PAH which include parasternal heave, palpable P₂, loud and single S₂, ejection murmur and early diastolic murmur from pulmonary area and no murmur from shunt lesion. ASD will have slightly differing clinical presentation—prominent JVP, cardiomegaly, hyperdynamic precordium and in a majority, split S₂ with loud P₂.

ECG in all conditions will show right axis deviation, right ventricular hypertrophy without strain pattern. qR in V1 or V3 is unlikely as RV pressure seldom crosses systemic levels.

GROUP IV CCHD

Increased PBF: Parallel Circulation

Transposition of great arteries (TGA) is the unique CHD belonging to this group. It will present with severe cyanosis and mild CHF—especially TGA with intact IVS. Clinical findings will be intense early cyanosis, mild cardiomegaly, mild CHF and minimal or no murmur. Murmur in this group will be due to associated PS, small VSD or PDA. Chest X-ray will show mild-moderate cardiomegaly, right atrial enlargement, RV contour, increased pulmonary vascular with narrow base.

ECG will show monotonous findings—right ventricular hypertrophy with RAD.

D-TGA with large VSD will behave with more CHF, severe PAH and less intense cyanosis. Similar clinical picture can occur in DORV. Subpulmonic VSD and PAH (Taussig-Bing anomaly).

GROUP V CCHD

Increased PBF: Admixture Lesions

If there is a complete mixing of systemic and pulmonary venous return due to a common mixing chamber, admixture lesions result. Single atrium, single ventricle and truncus arteriosus are the classical lesions. Total anomalous pulmonary venous connection (TAPVC) and DORV. VSD and PAH also belong to this group. Presentation includes CHF in infancy, mild cyanosis, cardiomegaly with hyperdynamic heart, evidence of PAH, abundant murmurs—systolic and diastolic; and growth failure. Clinically, they will behave similar to a large left to right shunt with mild cyanosis.

ASD like presentation; CHF; Cyanosis	- TAPVC. Single atrium
VSD like presentation: CHF; Cyanosis	- Single ventricle. DORV
PDA like presentation: CHF; Cyanosis	- Truncus

All these lesions will cause cardiomegaly and plethora of lung fields. TAPVC and single Atrium (pretricuspid lesions) will have significant right atrial enlargement. Post-tricuspid lesions—Single ventricle, DORV and Truncus will have LA enlargement or biatrial

enlargement. Truncus will have a right sided aortic arch in 40–50% of cases.

ECG in pretricuspid admixture lesions will have right axis deviation, right ventricular hypertrophy and frequently RSR pattern in V1 or V3R. In post-tricuspid lesions RAD, BVH are common.

Other CCHD

Some congenital heart diseases defy categorization in to any of the above groups. They include Ebstein anomaly, pulmonary AV fistula (PAVF). Ebstein anomaly will have early cyanosis, cardiomegaly, prominent JVP, split S₁ and S₂, S₃ and S₄ and murmurs. In ECG, Ebstein will show RAD, VSR or splintered QRS in V1-V2, occasionally WPW (Rt) syndrome. RVH is the exception. CXR will reveal cardiomegaly, pulmonary oligemia and right atrial enlargement. PAVF is a curious clinical entity which presents as cyanotic infant or child with minimal or no cardiac findings. CXR and ECG are most often normal. Echocardiographic anatomy of heart is also normal. A contrast echocardiography and later a pulmonary angiography needed to clinch the diagnosis. Salient features of TOF like clinical conditions with specific clinical findings are listed in **Table 4**.

CYANOTIC HEART DISEASE IN THE NEONATE

They will have resting saturation of less than 94% PO₂ of less than 75 mm Hg. The common CCHD and increased PBF in newborn are pulmonary atresia with VSD, severe TOF, and tricuspid atresia, pulmonary atresia with intact IVS, Ebstein anomaly and severe critical PS with reversal of atrial level. The common CCHD with increased flow in the neonate are truncus arteriosus, DORV, VSD, PAH, TAPVC and single ventricle. Simple TGA presents with intense cyanosis and is perhaps the most common CCHD in the new born period. PPHN is a major cause of central cyanosis in the neonate. A simple schema is available to identify CCHD in the neonate based on CXR and ECG (**Table 5**).

Table 4 TOF like clinical conditions with specific clinical findings

A	High volume pulse	<ul style="list-style-type: none"> • TOF with PDA/collaterals • PA with VSD with MAPCA • Truncus arteriosus with PS • TOF with BT shunt • TOF with AR
B	Prominent JVP	<ul style="list-style-type: none"> • Tricuspid atresia • AVSD with PS • TOF with prolapsed TV into VSD
C	Left ventricular apex	<ul style="list-style-type: none"> • Tricuspid atresia • Single ventricle • Truncus arteriosus (±)
D	Apical murmur	<ul style="list-style-type: none"> • L-TGA, VSD • AVSD with PS with MR, PS • Single ventricle ±

Abbreviations: RVH, right ventricular hypertrophy; LVH, left ventricular hypertrophy; BVH, biventricular hypertrophy; TOF, tetralogy of Fallot; PA, pulmonary atresia; VSD, ventricular septal defect; D-TGA, D-transposition of great arteries; PS, pulmonary stenosis; DORV, double outlet RV; IVS, intact VS; HRHS, hypoplastic right heart syndrome; SV, single ventricle; TAPVC, total anomalous pulmonary venous connection; DILV, double inlet left ventricle; PVH, pulmonary venous hypertension.

Table 5 Chest X-ray and ECG in the diagnosis of CCHD in children

Chest X-ray	Electrocardiographic findings		
	RVH	LVH	BVH
CXR: ↓PBF	TOF PA with VSD D-TGA. VSD. PS DORV. VSD. PS Severe PS SV. PS	P atresia. IVS tricuspid atresia HRHS (Some) SV. PS	SV. PS Truncus. PS.
CXR: ↑PBF/ Normal PBF	TGA. IVS TAPVC DORV. PAH SV. PAH HLHS	Tricuspid atresia DILV	Truncus DORV Single ventricle TGA. VSD
CXR: PVH	HLHS Obstructive TAPVC	-	-

Abbreviations: RVH, right ventricular hypertrophy; LVH, left ventricular hypertrophy; BVH, biventricular hypertrophy; TOF, tetralogy of Fallot; PA, pulmonary atresia; VSD, ventricular septal defect; D-TGA, D-transposition of great arteries; PS, pulmonary stenosis; DORV, double outlet RV; IVS, intact VS; HRHS, hypoplastic right heart syndrome; SV, single ventricle; TAPVC, total anomalous pulmonary venous connection; DILV, double inlet left ventricle; PVH, pulmonary venous hypertension.

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IN A NUTSHELL

1. Cyanotic children are first classified into those who have decreased pulmonary blood flow (↓PBF) or those with increased pulmonary blood flow (↑PBF). CCHD with reduced PBF can be further categorized into two major groups: (a) With pulmonic stenosis; and (b) With pulmonary hypertension.
2. CCHD can be further grouped in 5 distinct clinical presentations as follows:
 - a. *Group I:* Decreased PBF; PS with VSD (TOF)
 - b. *Group II:* Decreased PBF: Severe PS, intact interventricular septum (Valvar PS)
 - c. *Group III:* Decreased PBF, Pulmonary hypertension (Eisenmenger syndrome)
 - d. *Group IV:* Increased PBF, parallel circulation (TGA)
 - e. *Group V:* Increased PBF, admixture lesions (TAPVC).

Chapter 40.21

Tetralogy of Fallot and Variants

Anita Saxena

Tetralogy of Fallot (TOF) is the most common cyanotic congenital heart disease (CCHD) in patients beyond the neonatal period. It was named after Etienne-Louis Arthur Fallot, a French physician, who first described the anatomical details in 1888. TOF is characterized by four typical abnormalities, namely infundibular pulmonary stenosis (PS) or right ventricular outflow tract obstruction (RVOTO), large nonrestrictive subaortic ventricular septal defect (VSD), overriding aorta and right ventricular hypertrophy (RVH) (**Fig. 1**).

VARIANTS OF TETRALOGY OF FALLOT

Tetralogy of Fallot variants include other CCHDs associated with a nonrestrictive VSD and reduced pulmonary blood flow. These include (1) pulmonary atresia with VSD, (2) TOF with absent pulmonary valve, (3) TOF with atrioventricular septal defect (AVSD), and (4) TOF with double outlet right ventricle (DORV). This chapter deals with diagnosis and management of TOF and its variants.

CYANOTIC CONGENITAL HEART DISEASES WITH TOF PHYSIOLOGY

Other CCHDs like tricuspid atresia with PS (TAPS), single ventricle with PS (SVPS), Transposition of great arteries with VSD and PS (TGA,VSD and PS), corrected transposition of great arteries with VSD and PS (c-TGA,VSD and PS) and complex diseases such as heterotaxy syndrome associated with VSD and PS, are sometimes grouped together as TOF physiology. These will not be discussed in this chapter.

EPIDEMIOLOGY

Tetralogy of Fallot represents 5–10% of all CHDs. It is the most common cause of cyanosis beyond the first weeks of life. The natural history is quite variable; most cases are diagnosed early in life,

especially in western countries. In India and many other developing countries, it is not uncommon to see adolescents or adults with unrepaired TOF. It is estimated that as many as 7,500–9,000 babies are born with TOF every year in India. The sex distribution is nearly equal; a slight dominance is described for males.

ETIOLOGY AND RISK FACTORS

Chromosomal abnormality of 22q.11.2 deletion is present in 15% of TOF patients. The recurrent risk in siblings is approximately 2–3%, but increases to 8% if two or more siblings are affected. If one of the parents has TOF, the chance of having a baby with TOF is 3–4% in those without 22q.11.2 deletion. The other risk factors which may increase the chances of a baby born with TOF include maternal diabetes mellitus and consumption of retinoic acid or trimethadione during pregnancy. In vast majority of cases, however, the etiology remains unknown.

Syndromic TOF

In a small proportion of patients, TOF is seen in association with a cluster of noncardiac congenital abnormalities and hence these children are labeled as having syndromic TOF. The most common abnormality found in patients with syndromic TOF is micro deletion of 22q11.2, also known as DiGeorge syndrome or velocardiofacial syndrome. This syndrome is characterized by facial dysmorphism, neonatal hypocalcemia and several other defects. Another chromosomal abnormality in syndromic TOF is presence of Trisomy 21 or Down syndrome. In rare cases Edward syndrome (Trisomy 18) and Patau syndrome (Trisomy 13) may be associated with TOF. Nonsyndromic TOF is much more common and several gene mutations are being linked as the underlying etiology in these patients.

HEMODYNAMICS

All the four abnormalities described in TOF result from anterior and cephalad deviation of the outlet (infundibular) septum along with hypertrophied septoparietal trabeculations. The deviation of outlet septum results in narrowing of the infundibular region and a defect between the two ventricles. The VSD is malaligned due to the deviation of outlet septum causing aortic override. The pressures in right ventricle (RV) and left ventricle (LV) equalize due to a large VSD. This along with RVOTO results in RVH. Since the abnormality originates in fetal life, the flow across the right ventricular outflow tract and main pulmonary artery is reduced and hence pulmonary artery (PA) and its branches remain small or hypoplastic.

The blood flow increases across aortic valve dilating ascending aorta. In addition, inherent problems in the wall of the ascending aorta are described in patients with TOF. This further dilates aorta and may result in, at times, aortic regurgitation (AR). The degree of override of aorta varies from 20% to 90% and aortic root rotates rightward and clockwise. The aortic valve leaflet is in fibrous continuity with the anterior mitral valve leaflet as seen in normal population.

The degree of infundibular stenosis determines the clinical presentation. Associated valvar PS is also seen in a small proportion of cases. In extreme form of TOF, no antegrade flow occurs across the right ventricular outflow tract resulting in pulmonary atresia. Progression of infundibular stenosis to complete blockage of the orifice is well described in postnatal life. Peripheral pulmonary artery branch stenosis has been described in about 20–25% of patients with TOF. The stenosis often occurs at the ostia of left and right pulmonary arteries, the former is much more common. Constriction by ductus tissue at the site of ductal insertion in left pulmonary artery is responsible for most cases of ostial stenosis of left pulmonary artery.

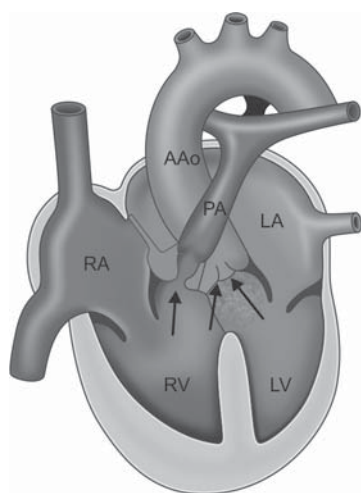


Figure 1 Diagrammatic representation of heart in tetralogy of Fallot showing a large ventricular septal defect, right ventricular outflow tract obstruction, overriding of aorta and right ventricular hypertrophy. Abbreviations: AAo, ascending aorta; LA, left atrium; LV, left ventricle; PA, pulmonary artery; RA, right atrium; RV, right ventricle.

The VSD is large, nonrestrictive and is subaortic in location, rarely it may be doubly committed and subarterial due to complete absence of infundibular septum. This type of VSD is more commonly described from South-East Asian population. Additional muscular VSDs are seen in a minority of patients. In those with Down syndrome, the VSD is located in the inlet region as a part of AVSD.

ANATOMIC VARIANTS OF FALLOT TETRALOGY

Tetralogy of Fallot with Pulmonary Atresia

This is the most severe form of TOF. In this condition there is no antegrade flow across the pulmonary valve, either because of complete infundibular atresia or due to pulmonary valve atresia. The pulmonary arteries are small or even absent. In about half of the cases, pulmonary blood flow is derived from patent ductus arteriosus and these usually have well-formed central pulmonary arteries. In the remaining half, the pulmonary blood flow is derived from systemic-to-pulmonary collaterals and central pulmonary arteries may be very small, seagull like, or completely absent. Large collaterals are also labeled as major aortopulmonary collateral arteries (MAPCAs) and these originate from descending thoracic aorta. Aortopulmonary collateral arteries can also arise from subclavian arteries. Large collateral arteries usually supply different segments of lungs with almost no overlap of blood supply. Stenosis in the course of collateral arteries is usual, thus protecting lungs against exposure to high systemic pressures.

Tetralogy of Fallot with Absent Pulmonary Valve

In about 5% of cases of TOF, the pulmonary valve leaflet tissue is absent or rudimentary. The RVOTO in such cases is due to pulmonary annulus hypoplasia with mild or no infundibular stenosis. The main and branch pulmonary arteries are dilated and may be aneurysmal. The enlarged pulmonary arteries tend to compress over the tracheobronchial tree producing marked respiratory symptoms. The ductus arteriosus is almost always absent. Right aortic arch is more common than in TOF, seen in 50% of cases. Free pulmonary regurgitation is universal. Associated abnormalities of tracheobronchial tree, including weakness of walls of airways, are known to be associated further aggravating the respiratory symptoms in these patients.

Tetralogy of Fallot with Double Outlet Right Ventricle (DORV)

In this variant, the aortic override is more than 50%. More than half of aorta is committed to right ventricle. Moreover, there is tissue interposed between the aortic valve and the anterior mitral valve leaflet, resulting in discontinuity between the two structures. The physiology and hemodynamics are not very different from that of TOF; however, the surgical repair may be somewhat different. These patients are more prone to develop left ventricular outflow tract narrowing postoperatively.

Tetralogy of Fallot with Atrioventricular Septal Defect

This combination is seen in 2% of TOF patients, mostly in those with Down syndrome. The information is important when closing VSD at the time of surgical repair. The ECG may show left axis deviation, a typical finding for AVSD.

ASSOCIATED ANOMALIES

Coronary Artery Anomalies

Coronary anomalies are seen in 5–8% of patients, the most important being anomalous origin of left anterior descending

artery (LAD) from right coronary artery (RCA). This abnormality, seen in 3–4% of cases, is ominous as the anomalous LAD crosses the right ventricular outflow tract when coursing towards left ventricle and is likely to get injured at the time of surgical repair if right ventriculotomy is done. Single coronary artery is a less common anomaly associated with TOF and one of its branches may pose a similar challenge during surgery.

Aortopulmonary Collaterals

Classically described in patients with pulmonary atresia and VSD, aortopulmonary collateral is not uncommon in TOF, especially in unrepaired adult patients. These develop mostly from bronchial arteries, but are also seen from subclavian arteries and very rarely from coronary arteries. Significant collaterals need to be occluded in the catheterization lab prior to surgical repair of TOF. Aortopulmonary collaterals are a source of nuisance when dealing with older children and adults with TOF. They can result in hemoptysis. Collaterals are also a source of bleeding in the intra- and postoperative period after intracardiac repair for TOF.

Right Aortic Arch

Right-sided aortic arch is seen in 25% of patients with TOF. The branching pattern is mirror image of the normal. The prevalence is higher in pulmonary atresia with VSD.

Others

Associations such as discontinuous pulmonary arteries, unilateral absence of a pulmonary artery branch, additional muscular VSDs, etc., have significant bearing on planning the surgical repair. Atrial septal defect, patent foramen ovale, partial anomalous pulmonary venous connection are also known to be associated with TOF but are of minor significance.

CLINICAL FEATURES

Tetralogy of Fallot produces no symptom or sign in fetal life although it can be diagnosed in a fetus using echocardiography. In most patients, variable degree of cyanosis is noticed in first few months of life. However, presentation may be delayed to a much older age, more so in developing countries. At times the first presentation is in a cyanotic spell. Some of the patients may be completely acyanotic and asymptomatic as the RVOTO is not very severe and hence good pulmonary blood flow is maintained. Such patients are labeled as Pink TOF. The symptomatic status of the patient is primarily determined by degree of RVOTO.

Those with severe obstruction present early and sometimes present in a cyanotic spell. A cyanotic spell is seen in patients aged between 6 months and 2 years and is characterized by deepening of cyanosis, faster and deep acidotic breathing and excessive irritability. A severe episode can produce convulsions, unconsciousness and even death. The precipitating events include crying and defecation. Anemia is a very important and common underlying precipitating factor in Indian setup. Cyanotic spell occurs secondary to tachycardia, decreased peripheral vascular resistance and infundibular spasm. Even one episode of cyanotic spell should be considered very significant and indicates early intervention. Anemia must be corrected by transfusing whole blood. Diagnosing anemia in a cyanotic child can be difficult on physical examination and hemoglobin (Hb) estimation can also be misleading. Cyanotic patients require a higher Hb and therefore an Hb of less than 13–14 g/dL should be considered low.

Older children, generally above 2 years of age assume squatting posture to combat hypoxia. Squatting is a very typical symptom of TOF and helps child to get relief since squatting increases peripheral vascular resistance and decreases right to left shunting.

Squatting also decreases the unsaturated blood from legs to reach heart. Squatting generally disappears by 8–10 years of age. In older children and adults, exercise limitation and exertional dyspnea are main symptoms, primarily related to hypoxemia.

Rarely, patients present with cerebral stroke. Stroke occurs secondary to cerebral infarct or cerebral abscess. Infarcts are more likely in younger patients (< 2 years of age) and are generally associated with iron deficiency anemia. Brain abscess is seen in older children and adults, secondary to an infection since bacteria can cross from right side of the heart to the left side of the heart. Brain abscess must be suspected in an older child or adult having TOF and presenting with history of fever, headache, listlessness, vomiting, etc., even without clear-cut neurological deficit.

Physical Signs

The growth and weight gain is often normal. Varying degree of cyanosis is seen (except in Pink TOF patients). In patients with syndromic TOF, facial features of DiGeorge syndrome or Down syndrome may be obvious. Clubbing of fingers and toes is noticeable in cyanotic patients; advanced grades of clubbing are seen in older children.

Features of heart failure are absent. In older patients, a wave may be prominent in jugular venous pressure. The cardiac impulse is placed normally with no evidence of cardiomegaly. A right ventricular heave is absent or is very soft. Systolic thrill along upper and mid left sternal edge may be felt, especially in those with mild cyanosis. On auscultation, second sound is single and there may be a constant ejection click due to a dilated aorta. The classical finding is presence of an ejection systolic murmur at upper and mid left sternal border. The intensity and duration of the murmur is inversely proportional to the severity of cyanosis. The murmur intensity can change and it may be absent during a cyanotic

spell. It is important to understand that VSD does not produce any murmur in these patients as pressures in both ventricles are equalized. A continuous murmur is suggestive of pulmonary atresia with VSD. The murmur if heard at the upper left sternal border is due to a patent ductus arteriosus (PDA) and if heard at the right upper sternal border or over the back, then it is due to aortopulmonary collaterals. A to and fro murmur (ejection systolic and early diastolic) at upper left sternal edge is very suggestive of TOF with absent pulmonary valve syndrome.

NATURAL HISTORY

One year survival for unoperated patients of TOF is close to 70%. 10-year survival varies from 20–25%, however, only 6% survive beyond 30 years. The survival is much poorer for pulmonary atresia with VSD, only 8% survive beyond 10 years. The disease is generally progressive due to increasing infundibular stenosis. The compliance of the right ventricle reduces as age advances, further increasing the right to left shunting. Aortic regurgitation develops in 5–7% of patients, either due to a dilated aorta (caused by increased blood flow and medial weakness of aortic wall), large aortopulmonary collaterals, aortic valve prolapse (in those with sub arterial VSD) or secondary to infective endocarditis of aortic valve. These patients also develop complications like coagulopathies, hyperuricemia, and skin, pulmonary and renal abnormalities which are related to prolonged hypoxemia, cyanosis and polycythemia.

INVESTIGATIONS

ECG

Characteristic findings of TOF are right axis deviation and right ventricular hypertrophy (**Fig. 2**). The precordial leads typically show early transition in leads V1 or V2 and therefore recording of

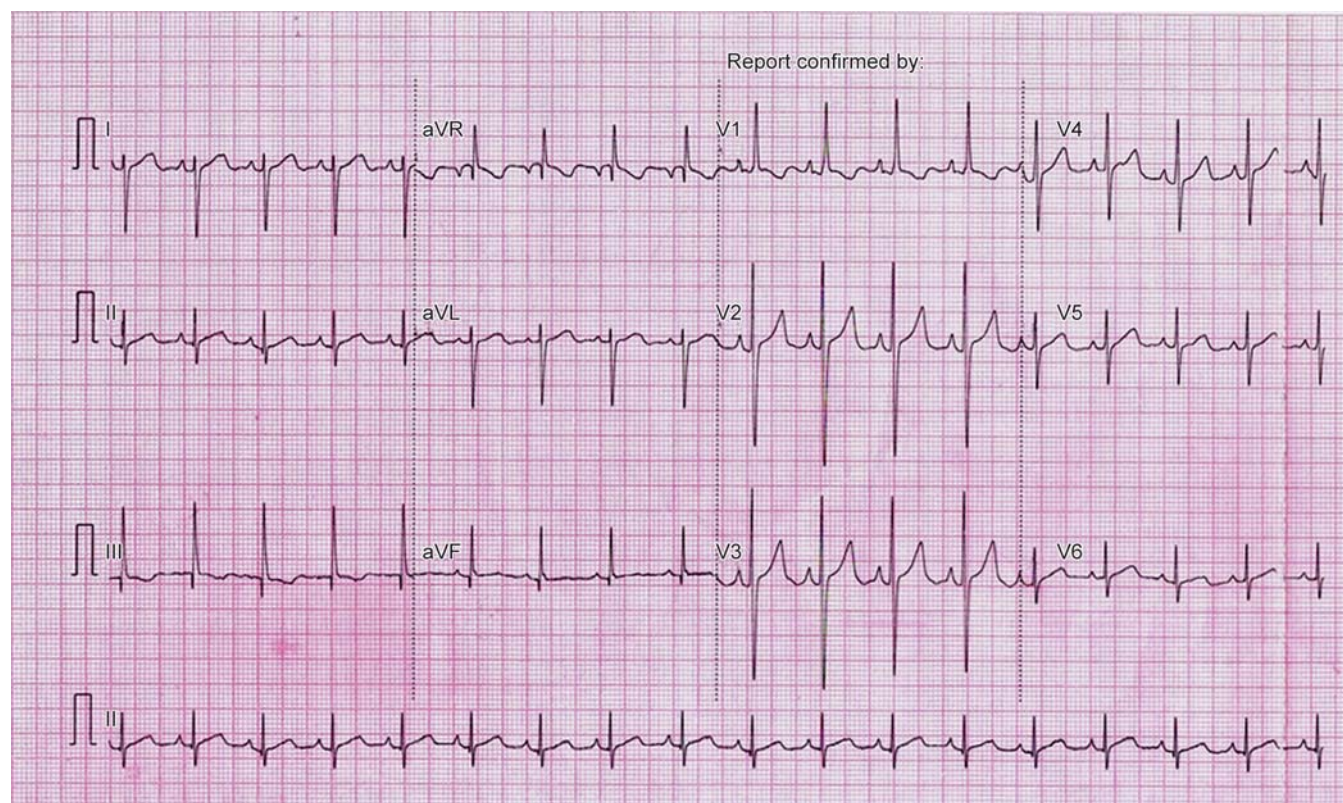


Figure 2 Electrocardiogram showing right axis deviation, right ventricular hypertrophy and early transition of QRS complexes in precordial leads

V₄R lead is advisable. Patients with AVSD variant may show left axis deviation of the QRS axis. Wide QRS with right bundle branch block pattern is sometimes seen after complete repair of TOF.

X-ray Chest

Normal cardiac size with uplifted apex, typical of hypertrophied right ventricle along with concave pulmonary artery segment gives a typical contour to the heart shadow, called boot-shaped heart (**Fig. 3**). Those with right sided aortic arch show an indentation to the right of tracheal shadow. The lung fields are oligemic in cyanotic patients. Patients with TOF and absent pulmonary valve may show cardiomegaly with or without pulmonary plethora. The central pulmonary arteries are dilated in these cases.

Echocardiography

It is the most important diagnostic tool and must be performed for each case. It establishes the diagnosis and may be able to provide full preoperative information in infants and young children with good acoustic windows. The size, location of VSD is well defined (**Fig. 4**). One must be careful when excluding additional muscular VSDs by echo as color Doppler may not be useful since pressures in the two ventricles are equal (**Figs 5A and B**). The anatomy of the right ventricular outflow tract, sizes of pulmonary annulus, and main, right and left pulmonary arteries can also be adequately assessed (**Figs 6A and B**). The gradient across the right ventricular outflow tract is easily estimated by Doppler (**Fig. 7**). In young infants, it may be possible to define coronary anatomy (**Fig. 8**) and aortopulmonary collaterals. Echo is also very useful modality during cardiac surgery as intraoperative transesophageal echo is able to detect additional VSDs better. It also confirms adequacy of repair when performed after completing surgery. Echocardiography has an important role in long-term follow-up of operated patients, especially for sequential follow up to determine timing of pulmonary valve replacement.

Echocardiography in patients with TOF with absent pulmonary valve shows dilated proximal pulmonary arteries, rudimentary pulmonary valve with stenosis at annular level (**Figs 9A and B**). Significant pulmonary regurgitation is seen on color Doppler (**Fig. 10**).

Cardiac Catheterization and Angiography

Cardiac catheterization and angiography is required as a part of preoperative work-up of those patients in whom full information

is not obtained by echocardiography. Cardiac catheterization and angiography has the added advantage of providing hemodynamic data and details of coronary anatomy, aortopulmonary collaterals and additional VSDs. Filling pressures on right and left side of heart provide important information about the diastolic function of the cardiac chambers. Angiograms are made in right ventricle to define its size, function and to delineate infundibular stenosis, main and branch pulmonary arteries (**Figs 11A and B**). Left ventricular angiography defines subaortic VSD, additional VSDs (if present) and also the degree of aortic override (**Fig. 12**). Aortic root angiogram provides information about coronaries; their origin and course (**Fig. 13**) and aortic regurgitation. Aortopulmonary collaterals are seen on descending thoracic aortogram. In older children and adults, it may be better to do selective injection into subclavian arteries to exclude collateral from these vessels. Significant collaterals need to be occluded in the catheterization lab prior to surgical repair of TOF, by use of commercially available coils and/or other materials (**Figs 14A and B**).

Magnetic Resonance Imaging (MRI)

This investigation is rarely performed, except in patients with pulmonary atresia and VSD. In these patients, MRI defines aortopulmonary collaterals well, prior to unifocalization surgery. MRI is indispensable for follow up of postsurgical TOF patients. Right ventricular volume and function, and quantification of pulmonary regurgitation are best estimated serially by MRI. It also helps to determine the timing of pulmonary valve replacement in these patients. Unfortunately with the presently available machines, MRI takes long time for image acquisition and is therefore not very suitable for infants and young children who would need general anesthesia for performing MRI.

CT Angiography

With advances in CT equipment, CT angio can be done very fast and with lower doses of radiations. CT angio is a good preoperative investigation in select cases where information on echo is not complete. It can provide useful information on pulmonary artery anatomy, coronaries and aortopulmonary collaterals.

MANAGEMENT

Every patient with TOF needs surgical repair, although at times complex anatomy may prohibit complete intracardiac repair.



Figure 3 Chest X-ray showing absence of cardiomegaly, right ventricular apex, concave pulmonary artery segment and pulmonary oligemia

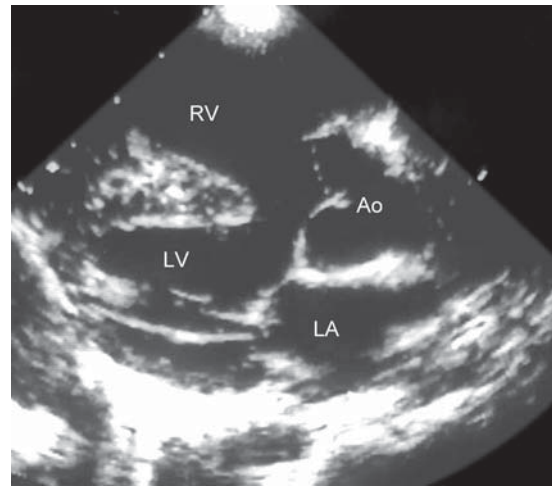
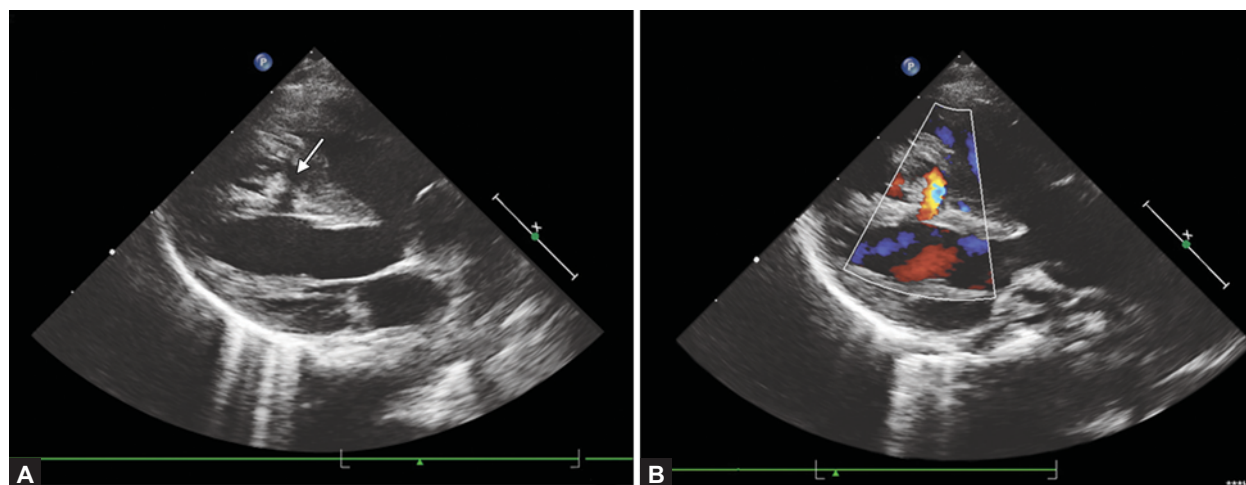
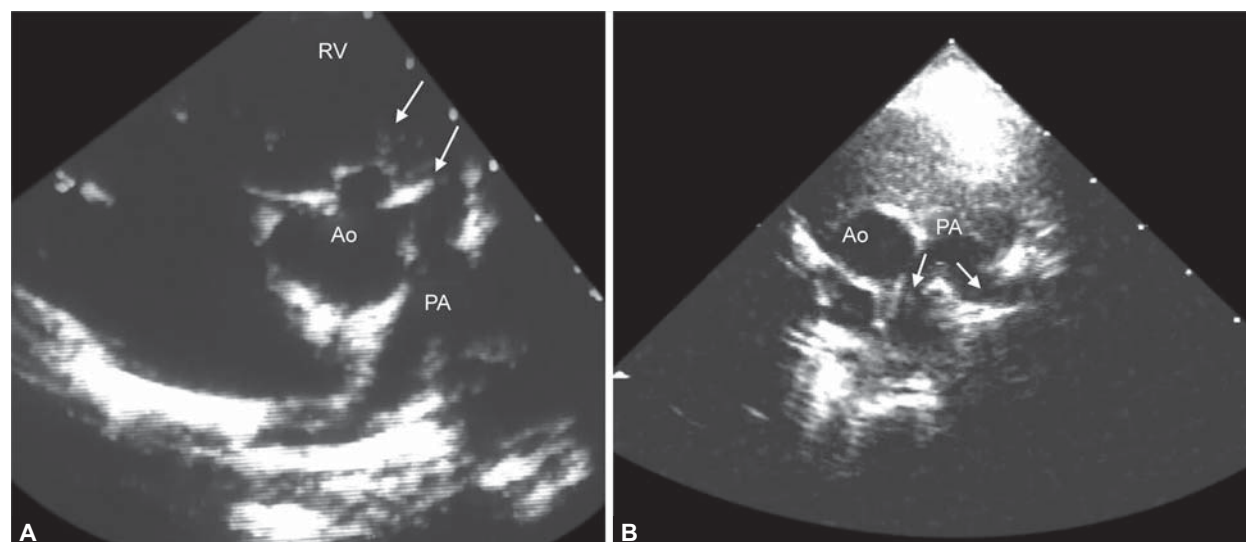


Figure 4 Echocardiogram in parasternal long axis view showing a large subaortic ventricular septal defect with aortic override
Abbreviations: Ao, aorta; LA, left atrium; LV, left ventricle; RV, right ventricle.



Figures 5A and B Echocardiogram in parasternal long axis view demonstrating an additional muscular ventricular septal defect (A) indicated by an arrow (B) and color flow across it



Figures 6A and B Echocardiogram in short axis view showing narrow right ventricular outflow tract (arrows in A) and right and left pulmonary arteries (arrows in B)

Abbreviations: Ao, aorta; PA, pulmonary artery; RV, right ventricle.

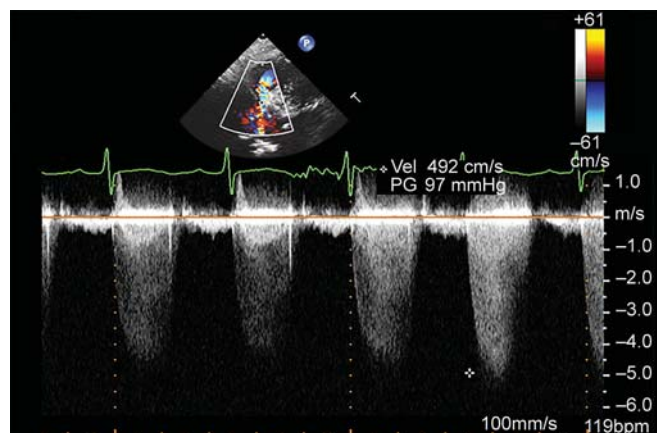
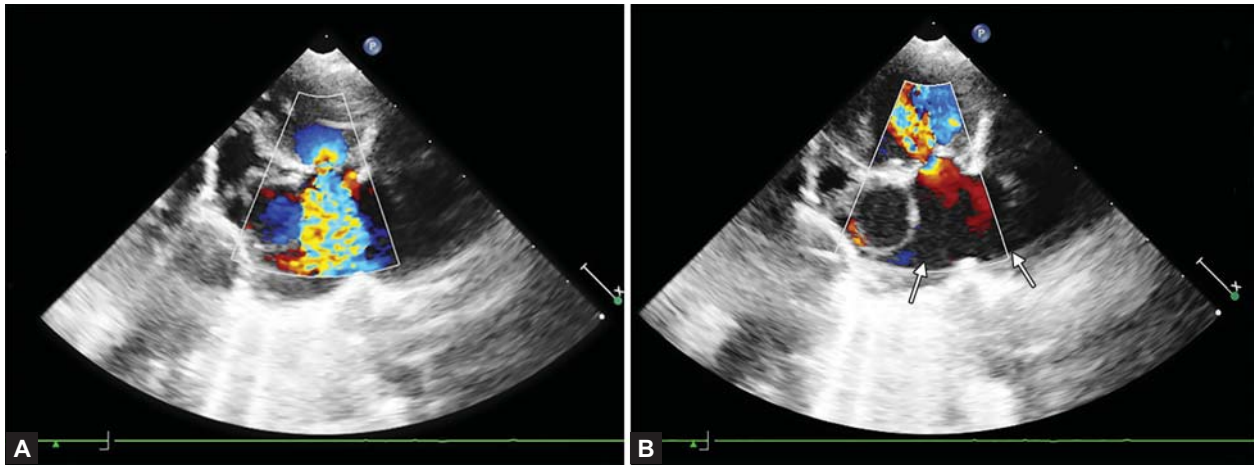


Figure 7 Doppler signal across right ventricular outflow tract showing a gradient of 97 mm Hg across



Figure 8 High parasternal view on echocardiography in an infant, demonstrating right and left coronary arteries origin from aorta
Abbreviations: Ao, aorta; LCA, left coronary artery; RCA, right coronary artery.



Figures 9A and B Echocardiogram in parasternal short axis view from a patient of tetralogy of Fallot with absent pulmonary valve showing turbulence due to pulmonary stenosis (A) and pulmonary regurgitation, (B) note dilated right and left pulmonary artery branches (white arrows)

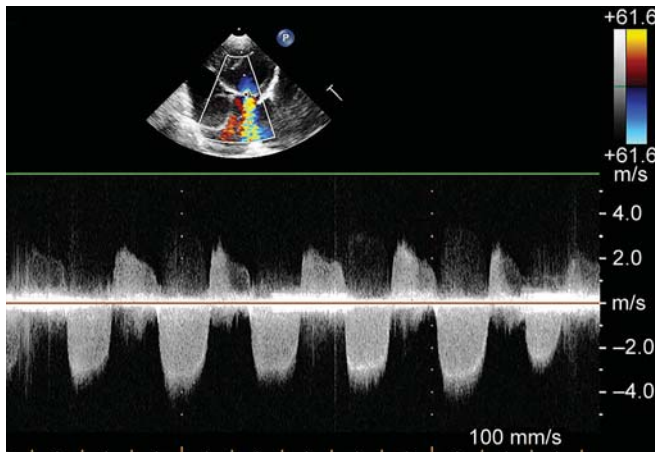


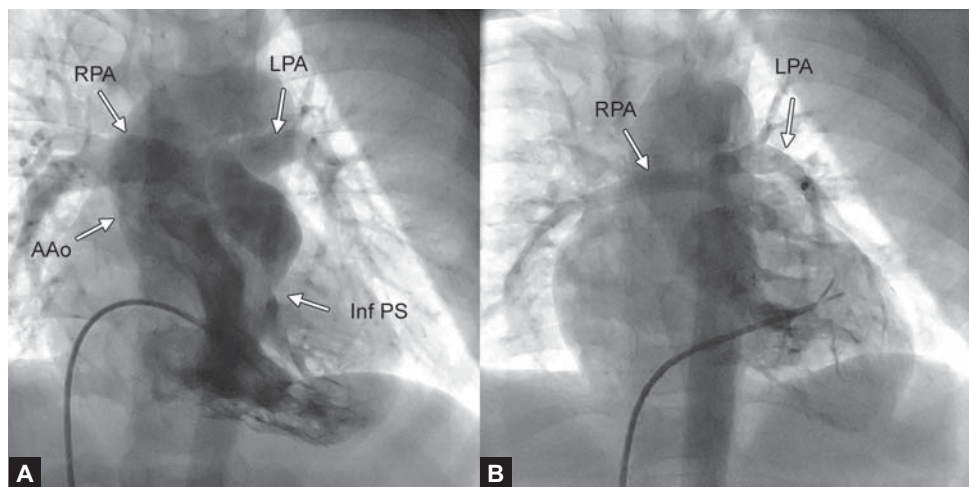
Figure 10 Doppler echo showing pulmonary stenosis and pulmonary regurgitation signals

Medial Management

With advances in surgical techniques, surgery is now being offered to infants and small children. Therefore, the role of medical management is limited. However in countries like India where surgical facilities are not widely available, medial management assumes importance till the time patient is operated.

Intravenous Prostaglandin

Intravenous prostaglandin (PGE1) maintains patency of ductus arteriosus when used in newborns. Continuous infusion at a dose of 0.05–0.4 $\mu\text{g}/\text{kg}/\text{min}$ is very useful for neonates with pulmonary atresia and VSD who become hypoxemic due to ductal closure. The PGE1 infusion is continued to maintain pulmonary blood flow till a systemic to pulmonary artery shunt surgery is done. It is important to remember that PGE1 can produce apnea in 10–15% of babies and hence must be given carefully in hospital setting with facilities for assisted ventilation.



Figures 11A and B Right ventricular angiogram from two patients of tetralogy of Fallot. Tight infundibular stenosis (inf PS) with adequate sized pulmonary arteries is seen (A) (B) Filling of very small pulmonary artery branches. Note filling of aorta due to the presence of right to left shunting through the ventricular septal defect

Abbreviations: AAo, ascending aorta; LPA, left pulmonary artery, RPA, right pulmonary artery.

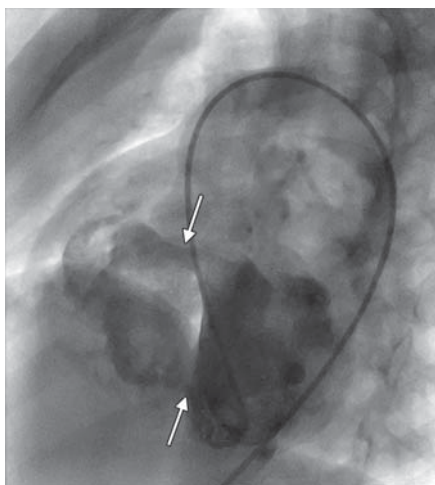


Figure 12 Left ventricular angiogram showing two ventricular septal defects (arrows), upper one is subaortic and lower one is muscular in location

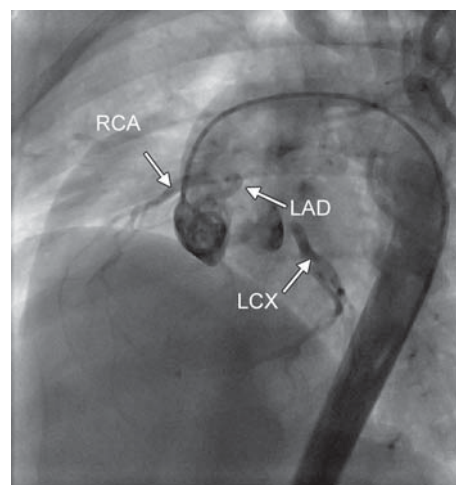
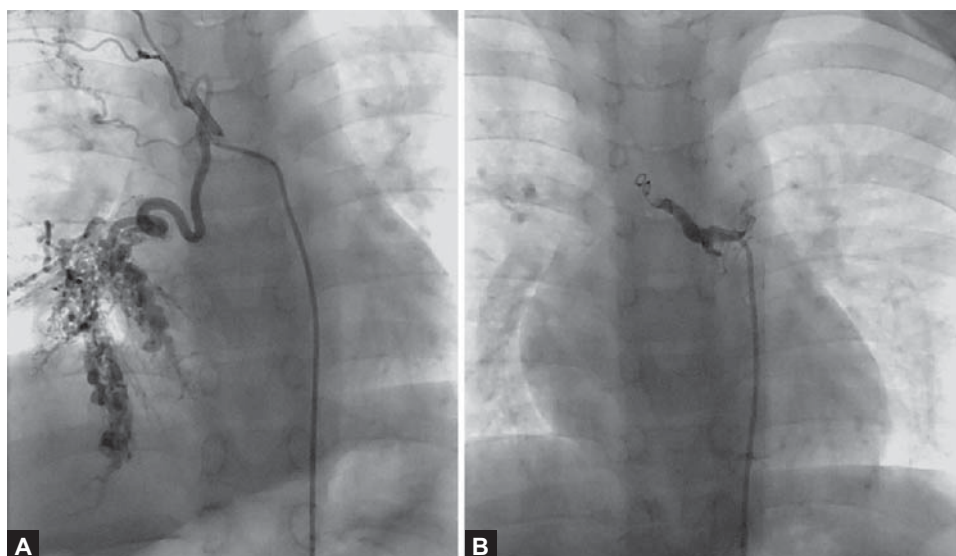


Figure 13 Aortic root angiogram demonstrating anomalous origin of left anterior descending (LAD) from right coronary artery (RCA). The left circumflex (LCX) coronary artery originates normally



Figures 14A and B Selective angiogram in an aortopulmonary collateral artery, before (A) and after (B) its occlusion with coils

Beta-blockers

These drugs are used to reduce heart rate and to relax dynamic component of infundibular stenosis. Propranolol is the most frequently used beta-blocker, the dose is 1–4 mg/kg/day in 3 divided doses.

Correction of Anemia

Iron supplements or even blood transfusion is necessary for correcting anemia which is a common finding in Indian setting.

Treatment of a Cyanotic Spell (Also see Chapter 40.38)

The spell should be managed as an emergency. Child is placed in a knee chest or squatting position and oxygen inhalation given. Morphine sulfate is injected intravenously (or subcutaneously if intravenous line is not available) in a dose of 0.1 mg/kg. Beta-blockers should be given intravenously. Propranolol or metoprolol may be used in a dose of 0.1 mg/kg, slow bolus. Heart rate and blood pressure should be monitored while giving beta-

blockers. The dose can be repeated after 5–7 min, if necessary. A vasoconstrictor drug such as phenylephrine is administered to increase peripheral vascular resistance, thereby decreasing right to left shunt. Child may be given sodium bicarbonate to counter acidosis. Intravenous fluids are given to expand volume; fluids can be given liberally since the risk of developing heart failure is almost negligible. If spell is still not aborted with these measures, child may be intubated and mechanically ventilated and urgent intervention performed.

Transcatheter Palliation

Some of the infants benefit from pulmonary valve balloon dilatation, especially if the RVOTO is both valvar and infundibular. Other modes of transcatheter treatment for select patients include stenting of ductus arteriosus (for pulmonary atresia variant) and stenting of right ventricular outflow tract. All these measures increase pulmonary blood flow instantly and give grace period before complete repair is undertaken.

Surgical Management

Complete surgical repair of TOF is the definitive treatment. The timing of complete intracardiac repair varies from center to center. If good surgical results can be attained with low operative mortality, morbidity, good medium and long-term outcomes, complete repair should be encouraged. However, a systemic to pulmonary artery shunt should be considered an option for infants and small children in centers where results of intracardiac repair are not optimal at this age. Management strategies producing the best outcome in their own institution should be pursued by treating physicians and surgeons.

Palliative Systemic Artery to Pulmonary Artery Shunt Procedure

In this procedure, an anastomosis is established between a systemic artery and same side branch pulmonary artery. The commonly performed shunt is Blalock-Taussig (BT) shunt, wherein subclavian artery is connected to ipsilateral branch pulmonary artery. This anastomosis may be direct (classical BT shunt) or by use of a Gore-Tex tube (modified BT shunt), modified BT shunt is usually performed these days. This procedure may be ideal for severely cyanosed patients, less than 4–6 months of age. The systemic saturation generally improves to over 80% following a BT shunt. BT shunts may also have to be done in older patients if the anatomy is not suitable for total repair. For example, in those with small pulmonary arteries, BT shunt helps in growth of pulmonary arteries. BT shunt is also indicated in children under 2–3 years of age who have an anomalous LAD from RCA and require transannular patch.

Total Intracardiac Repair

Although total repair can be done in neonatal period, most centers in India would do the repair in infants over 6 months or so of age. Elective repair in a stable patient can be performed at about one to one and a half years of age, at a body weight of over 7 kg. The VSD is closed using a patch; the muscle bundle in the infundibular region is resected to relieve RVOTO. Most of intracardiac repairs can be done using transatrial route combined with a transpulmonary approach and without the need of right ventriculotomy.

Patients with pulmonary atresia and sizable pulmonary arteries can undergo complete repair with the use of right ventricle to pulmonary artery conduit, along with closure of VSD. However cases where pulmonary arteries are absent or very small, the collaterals are used as pulmonary arteries and connected by a prosthetic tube to each other and to the right ventricle, this procedure is called unifocalization and may have to be performed in several stages. Surgical treatment of TOF with absent pulmonary valve usually requires a pulmonary valve replacement using a homograft and reduction of the dilated pulmonary arteries along with closure of VSD.

Surgical mortality for intracardiac repair is less than 2%. In some institutions it may be almost zero. Immediate and in-hospital

complications include development of complete heart block, atrial tachycardia, residual VSD, residual RVOTO, etc. Complete heart block is permanent in about 1% of patients operated for TOF requiring placement of a permanent pacemaker. Atrial tachycardia is treated with drugs; these are generally required for a short period. In view of increasing avoidance of right ventriculotomy, right bundle branch block pattern in the ECG is becoming less common.

LONG-TERM FOLLOW-UP

Long-term prognosis for patients operated for TOF is generally good; although survival is less than that of normal population (86% survival at 30 years). Pulmonary regurgitation is the major cause of late re-intervention. Pulmonary regurgitation results in right ventricular dilatation leading to impaired exercise tolerance, cardiac arrhythmia and increased risk of sudden death.

IN A NUTSHELL

1. Tetralogy of Fallot (TOF) is the most common cyanotic form of CHD.
2. The age at presentation varies depending upon the severity of RVOTO and degree of cyanosis.
3. Severe cyanosis may result in a cyanotic spell, which may be life-threatening.
4. The ECG and X-ray chest are quite characteristic and echocardiography is generally sufficient for defining the anatomy preoperatively.
5. In older children and adults, cardiac catheterization and angiography may be required prior to surgery.
6. Open heart surgery for intracardiac repair is the definite treatment.
7. In neonates and young infants, a palliative systemic to pulmonary artery shunt may have to be performed before a total repair can be undertaken.
8. In most instances long-term prognosis is good although lifelong follow-up is required.

MORE ON THIS TOPIC

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Chapter 40.22

Tricuspid Atresia

P Syamasundar Rao

Tricuspid atresia (TA) is defined as congenital absence or agenesis of the tricuspid valve. It is the third most common cyanotic congenital heart defect (CCHD) and is the most common cause of cyanosis with left ventricular hypertrophy.

EPIDEMIOLOGY

The reported prevalence of tricuspid atresia is 1.4% of all congenital heart defects (CHD). With known prevalence of CHDs at 0.8% of livebirths, tricuspid atresia is likely to occur in roughly 1 per 10,000 livebirths with no reported regional differences in Western and South Asian countries including India. Racial predilection is also not evidenced from available reports. When there is no sex predilection in the overall occurrence of TA as a whole, a male preponderance (66% versus 34%) is evident when both TA and transposition of the great arteries (TGA) occur in the same child.

ETIOLOGY

The etiology of TA is likely to be multifactorial as in other CHDs, wherein exposure of a sensitive fetus (genetically predisposed) to an adverse environmental trigger during a critical period of cardiac morphogenesis causes the CHD. Extensive studies of gene mapping that are currently in progress may unravel previously unknown genetic mechanisms.

PATHOGENESIS

The tricuspid valve (TV) develops shortly after the division of the atrioventricular canal. The septal leaflet of the tricuspid valve develops mostly from the inferior endocardial cushion. The anterior and posterior tricuspid valve leaflets appear to develop by undermining of a skirt of ventricular muscle tissue. The undermining process extends until the atrioventricular valve junction is reached. Resorption of the muscle tissue produces normal-appearing valve leaflets and chordae tendineae. Complete fusion of valve leaflet components results in tricuspid atresia (TA) while its partial fusion causes tricuspid stenosis (TS). The stage of development of the embryo when the environmental insult occurs determines the formation of either a muscular type of TA (most common form) or well-formed but fused tricuspid-valve leaflets.

CLASSIFICATION

Based on the Valve Morphology (Proposed first by Van Praagh and subsequently modified).

The most common type of tricuspid atresia (89%) is muscular, and it is characterized by a dimple or a localized fibrous thickening in the floor of the right atrium at the anticipated site of the tricuspid valve. Other less common types are rare.

Classification Based on Pulmonary Vascular Markings on a Chest Radiograph (Proposed by Astley and modified later by Dick).

Group A: Decreased pulmonary vascular markings

Group B: Increased pulmonary vascular markings and

Group C: Transition from increased to decreased pulmonary vascular markings.

Classification Based on Great-Artery Relationships (Proposed by Kühne and subsequently expanded and revised by Edwards and

Burchell, Keith, Rowe, and Vlad and Rao)

Type I: Normally related great arteries

Type II: D-Transposition of the great arteries

Type III: Great artery positional abnormalities other than D-transposition of the great arteries

- *Subtype 1* L-Transposition of the great arteries
- *Subtype 2* Double outlet right ventricle
- *Subtype 3* Double outlet left ventricle
- *Subtype 4* D-malposition of the great arteries (anatomically corrected malposition)
- *Subtype 5* L-malposition of the great arteries (anatomically corrected malposition)

Type IV: Persistent truncus arteriosus.

All types and subtypes are subdivided into the following subgroups:

- *Subgroup a:* Pulmonary atresia
- *Subgroup b:* Pulmonary stenosis or hypoplasia
- *Subgroup c:* No pulmonary stenosis (normal pulmonary arteries).

After the above categorization, the status of the ventricular septum [intact or ventricular septal defect (VSD)] and the presence of other associated defects are described.

HEMODYNAMICS

The atretic tricuspid valve necessitates the flow of all systemic venous blood across the atrial septum into the left atrium, from where it passes through the mitral valve into the left ventricle. This pattern of flow is similar in all except in type III subtypes 1 and 5. In these subtypes, the atretic morphologic TV is on the left side because of inverted ventricles. Consequently, the pathophysiology is that of mitral atresia with left-to-right shunting of pulmonary venous return and subsequent mixing with systemic venous return.

In children with type I TA with normally related great arteries and a VSD, left to right shunt across the VSD provides pulmonary blood flow, whereas in the absence of a VSD, the pulmonary blood flow essential for the very survival of the child is derived via the patent ductus arteriosus or aortopulmonary collateral vessels. The systemic blood flow is derived directly from the left ventricle.

In children with type II TA with D-transposition of the great arteries, the pulmonary blood flow is derived directly from the left ventricle. The aorta receives blood from the right ventricle via the VSD and left ventricle.

In other types of TA, the systemic and pulmonary artery flow are dependent on the ventriculoarterial relationship and the size of the VSD. Arterial desaturation occurs secondary to complete admixture of both pulmonary and systemic venous returns in the left atrium. Other physiologic principle includes volume overload of the left ventricle that has to supply the systemic, coronary and pulmonary circulations. Quantity of pulmonary blood flow is the main determining factor of the clinical presentation and subsequent therapeutic interventional measures.

It becomes absolutely essential to remember that the clinical features of TA are further influenced by the changing hemodynamics seen in growing infants. These include: (A) spontaneous closure of the ductus arteriosus causing pulmonary oligemia and systemic hypoxemia; (B) development of restriction of the interatrial communication, causing systemic venous congestion; and (C) spontaneous diminution or even complete closure of a VSD which may decrease pulmonary blood flow with consequent systemic hypoxemia in type I patients or produces subaortic (i.e., systemic) outflow obstruction in type II patients.

CLINICAL FEATURES

Nearly 50% of children with TA present with symptoms on their first day of life and 80% become symptomatic by the end of one month. The amount of pulmonary blood flow mainly determines the clinical features and the age of presentation.

Infants with Decreased Pulmonary Blood Flow

These children present with cyanosis in the first few days of life; the lesser the amount of pulmonary flow, the earlier the infant presents with cyanosis. Hyperpnea with acidotic breathing is often seen as presenting features besides cyanosis in these neonates with markedly decreased pulmonary blood flow. Most of these neonates are of type Ib classification mentioned above. In the presence of pulmonary atresia is (subgroup a), cyanosis gets manifest as the ductus begins to close.

Physical examination shows central cyanosis, tachypnea or hyperpnea, normal pulses, and no hepatomegaly are the usual features. The precordium is quiet without any thrills on palpation. On auscultation, the second heart sound is single, and a holosystolic murmur, suggestive of VSD is heard at the lower sternal border. Diastolic murmurs are not usually present. In cases with pulmonary atresia, no holosystolic murmur is heard, and a continuous murmur of patent ductus arteriosus is rarely heard. It is of note that signs of heart failure are absent.

Patients with Increased Pulmonary Blood Flow

These children present with symptoms suggestive of congestive heart failure, namely, dyspnea, fatigue, difficulty in feeding, and perspiration. Other modes of presentation are failure to thrive and recurrent respiratory tract infection. These symptoms usually occur within several weeks of life; however, some babies may present within the first week of life. Most of these babies belong to type IIc (i.e., transposition of the great arteries without pulmonary stenosis, but with VSD); some may be of type Ic (i.e., normally related great arteries and no pulmonary stenosis and a large VSD). Some babies with type II defect may have coarctation of the aorta and in such a situation the onset of congestive heart failure is early.

Physical examination reveals an infant with tachypnea, tachycardia, minimal cyanosis (if any), decreased femoral pulse (in the presence of aortic coarctation), hyperdynamic precordial impulses, single or split second heart sound, a third heart sound at the apex, holosystolic murmur of VSD at the left lower sternal border and a mid-diastolic rumble at the apex. Clinical signs of congestive heart failure are usually seen.

Other Features

In both the above two groups, prominent a waves in the jugular venous pulse along with prominent hepatic pulsation may be seen if clinically significant interatrial obstruction is present.

In a few patients who have balanced circulation without significant pulmonary oligemia or plethora, the presentation may be delayed and may present later with either a murmur or cyanosis.

Untreated patients may present with clubbing, polycythemia, stroke, brain abscess, coagulation abnormalities, and hyperuricemia; these are not too dissimilar to those seen in other cyanotic congenital heart defects. Older children and adolescents (and even adults) may present with atrial arrhythmias (flutter and/or fibrillation).

APPROACH TO DIAGNOSIS

A diagnosis of TA may be entertained by correlation of history of presentation with elicited clinical features and investigative

tools—chest X-ray and electrocardiogram (ECG) with subsequent confirmation by echocardiographic evaluation.

Chest X-ray

Its usefulness is in evaluating the pulmonary blood flow pattern and thus categorizing the index case to either CCHD with decreased pulmonary blood flow (oligemic lung fields) or CCHD with increased pulmonary blood flow (plethoric lung fields). In children with decreased pulmonary blood flow, the heart is normal in size or minimally enlarged. Concavity in the region of the pulmonary artery segment is seen in patients with a small pulmonary artery or pulmonary atresia. If pulmonary blood flow is increased, cardiac enlargement is seen.

Electrocardiogram

In an infant with cyanosis, ECG is virtually diagnostic of tricuspid atresia (**Fig. 1**). An abnormal and superiorly oriented major QRS vector, the so-called left axis deviation in the frontal plane, left ventricular hypertrophy, and decreased right ventricular forces are seen. Right atrial hypertrophy, evidenced by tall and peaked P waves (≥ 2.5 mm) in lead II and right chest leads may be present.

Echocardiogram and Doppler

Apical four-chambered and subcostal views help to identify the atretic tricuspid valve (TV), seen as a dense band of echoes at the site where the TV ought to be (**Figs 2A and B**); the right atrium, left atrium and left ventricle are enlarged whereas the right ventricle is usually small. The size of the left atrium and the size and function of the left ventricle can be assessed by echo studies.

Right to left shunt across the patent foramen ovale is seen by color Doppler imaging (**Fig. 3**). As mentioned above, TA is classified based on the relationship of the great arteries. Great artery relationship is established by following the vessel until bifurcation (**Figs 4A and B**) or aortic arch. In patients with normally related great arteries (type I), the VSD provides blood flow into the lungs (**Figs 5A to C**) while in those with associated transposition (type II), the VSD provides systemic flow.

Doppler Interrogation (Pulsed, Continuous Wave and Color Doppler)

It is also useful in demonstrating left to right shunt across the VSD (**Fig. 5**). Peak Doppler flow velocity across right ventricular outflow tract will help in identifying obstruction across these sites. As VSD may be small to cause obstruction to systemic flow, assessment of the size of VSD by 2D and color Doppler, pulsed and continuous wave Doppler is of paramount importance in type II patients. Imaging and Doppler from suprasternal notch view may show aortic coarctation (**Figs 6A and B**), which is more common in type II patients with transposition of the great arteries. The echo-Doppler findings are sufficiently characteristic for TA and therefore, cardiac catheterization and selective cineangiography are not needed for its diagnosis.

Other Laboratory Studies

Pulse oximetry measures systemic arterial oxygen saturation and is a useful adjunct in the clinical assessment. O_2 saturations in high 70s to low 80s are considered appropriate for tricuspid atresia. Arterial blood gases, in addition to assessment of oxygenation status, provide ventilatory status (i.e., PCO_2), and metabolic status (i.e., base deficit). Hemoglobin and hematocrit measurements along with RBC indices help to assess whether iron-deficiency anemia is present. Serum electrolytes are particularly useful in children receiving diuretics.

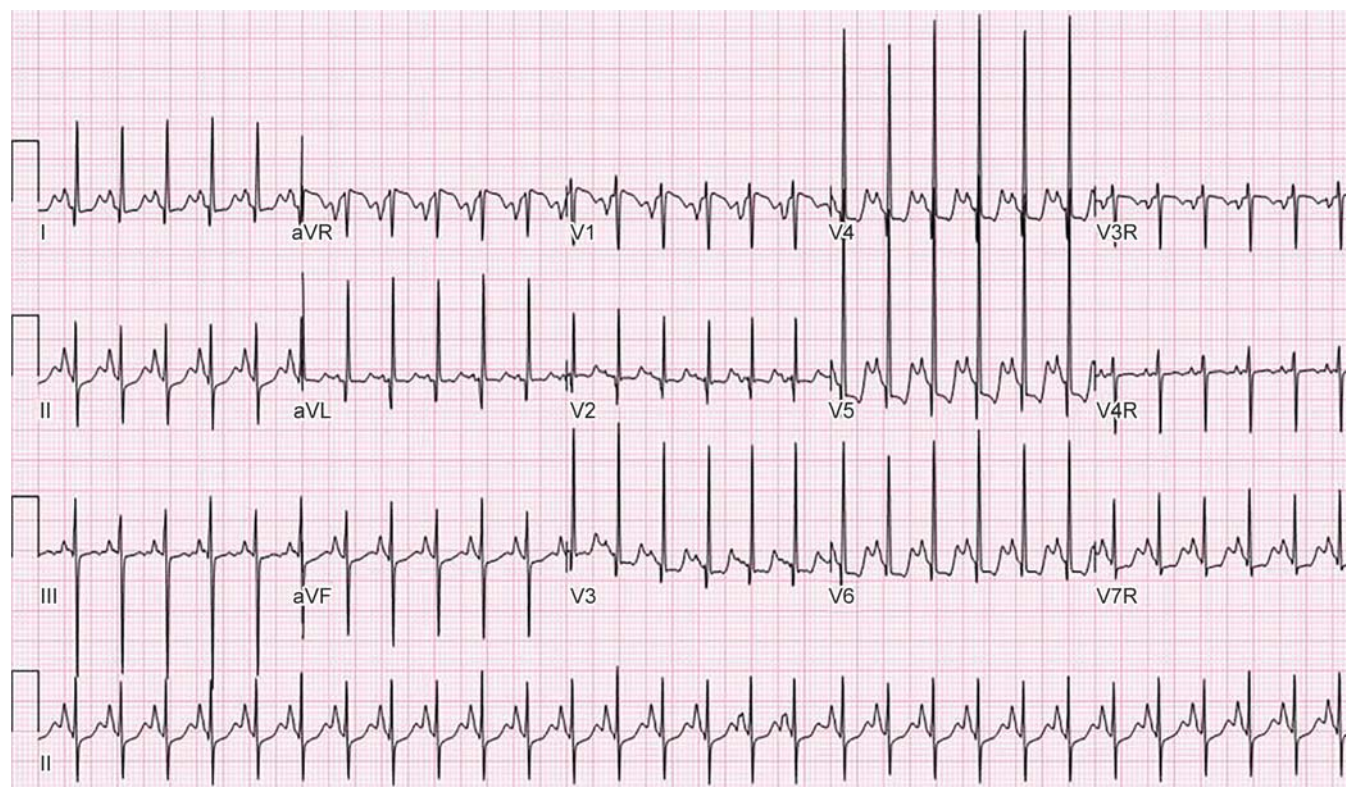
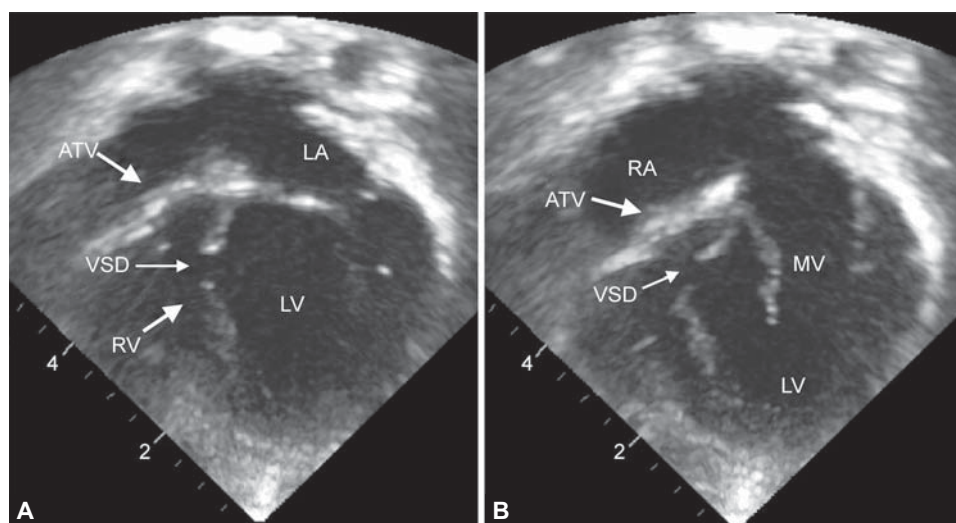


Figure 1 ECG of infant with tricuspid atresia showing abnormal, superiorly oriented mean QRS vector in frontal plane (-45° , left axis deviation), left ventricular hypertrophy, and diminished anterior (R waves in leads V1 and V2) and rightward (S waves in leads V5 and V6) forces. Prominent P waves, indicative of biatrial enlargement are also seen in several leads



Figures 2A and B Selected video frames from apical four-chamber, 2-dimensional echocardiographic views of a baby with tricuspid atresia demonstrating an enlarged left ventricle (LV), a small right ventricle (RV) and a dense band of echoes at the site where the tricuspid valve echo should be (ATV) (thick arrow) with closed (A) and open (B) mitral valve. A moderate sized ventricular septal defect (VSD) (thin arrow) is shown
Abbreviations: LA, left atrium; RA, right atrium.

Cardiac Catheterization

Cardiac catheterization and selective cineangiography are not necessary for diagnosis; however, such procedures are necessary during staged Fontan surgery. Prior to bidirectional Glenn (stage II), and Fontan (stage III), catheter evaluation is undertaken to define the pulmonary artery pressure and anatomy, to exclude

a persistent left superior vena cava (because it may divert blood away from the pulmonary arteries) and exclude risk factor for poor outcome. The latter are elevated pulmonary artery pressure (mean pressure, > 18 mm Hg) or resistance (> 4 Wood units/ m^2), distorted or small (McGoan ratio of 1.8 or less) pulmonary arteries, poor left ventricular function (end-diastolic pressure above 12 mm Hg),

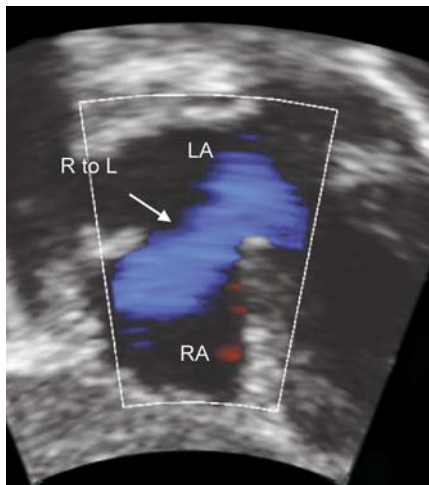


Figure 3 Selected video frame from subcostal view of an infant with tricuspid atresia demonstrating right-to-left (R to L) shunt (arrow) across the interatrial communication
Abbreviations: LA, left atrium; RA, right atrium.

significant mitral regurgitation, subaortic obstruction, and severe left ventricular hypertrophy. At the same time, aortopulmonary collaterals should be evaluated by means of selective subclavian artery and descending thoracic aortic angiography. If collateral vessels are present, they should be occluded with coils or devices, as appropriate.

DIFFERENTIAL DIAGNOSES

There are many other cardiac defects that cause cyanosis or congestive heart failure. The differential diagnosis is largely based on evaluation of pulmonary blood flow on a chest roentgenogram.

Decreased Pulmonary Vascular Markings

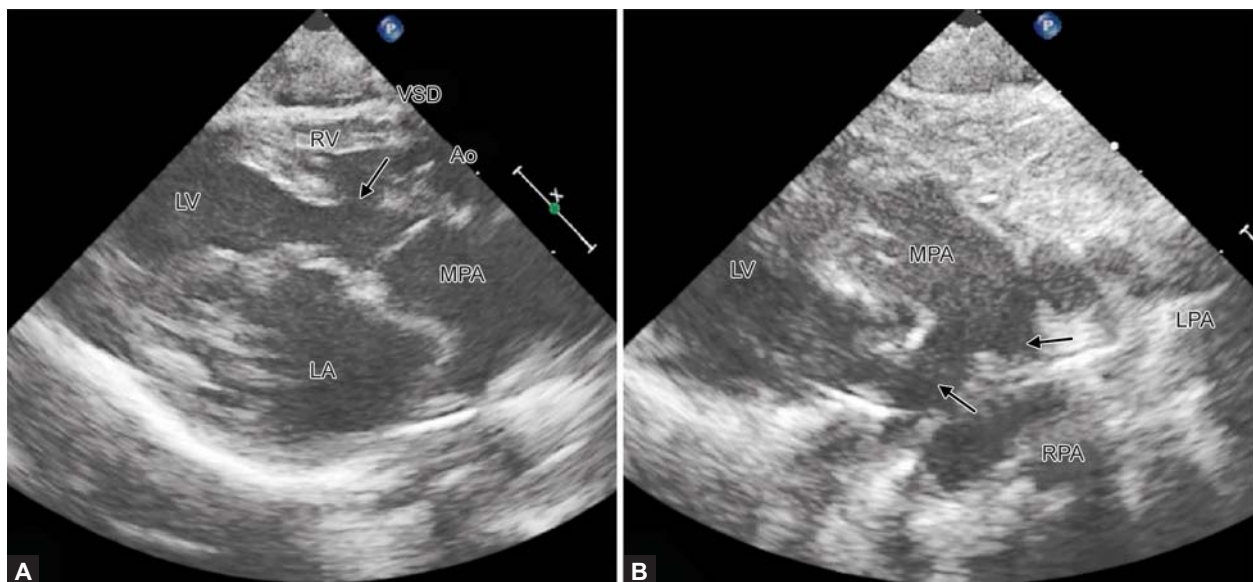
The most frequently encountered CHDs in this group are tetralogy of Fallot (TOF), pulmonary atresia with intact ventricular septum and complex cyanotic CHD with pulmonary stenosis or atresia. Differential diagnosis of these infants can be made by analysis of the electrocardiogram (ECG) (**Fig. 7**). Patients with tetralogy of Fallot exhibit right axis deviation ($+90$ to $\pm 180^\circ$) in the ECG; right ventricular hypertrophy may also be present. Infants with pulmonary atresia with intact ventricular septum are likely to have an axis of 0 to $+90^\circ$. The R waves in leads V1 and V2 and S waves in leads V5 and V6 (right ventricular voltages) are decreased and left ventricular hypertrophy (LVH) may be seen. Children with TA, on the other hand exhibit LAD (superior vector) 0 to -90° . They may have LVH and decreased right ventricular voltages. The final group with complex pulmonary stenosis includes cyanotic heart defects such as single ventricle, double outlet right ventricle, ventricular inversion and others, all associated with severe pulmonary stenosis or atresia. The axis and ventricular hypertrophy patterns in the ECG vary markedly in this subgroup. Each of the above defects has characteristic echocardiographic features and the diagnosis may be confirmed by echo.

Increased Pulmonary Vascular Markings

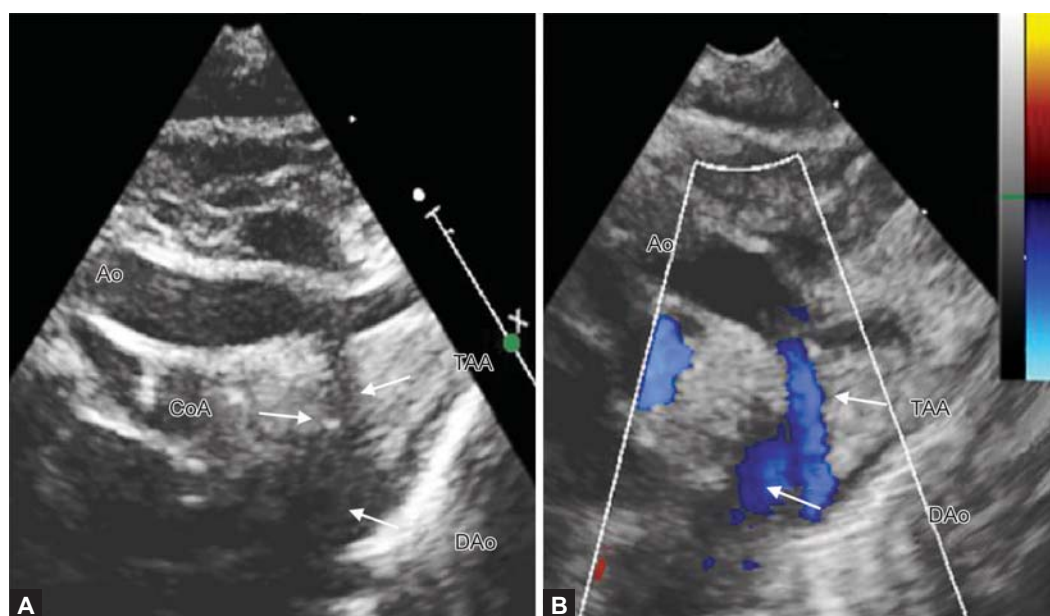
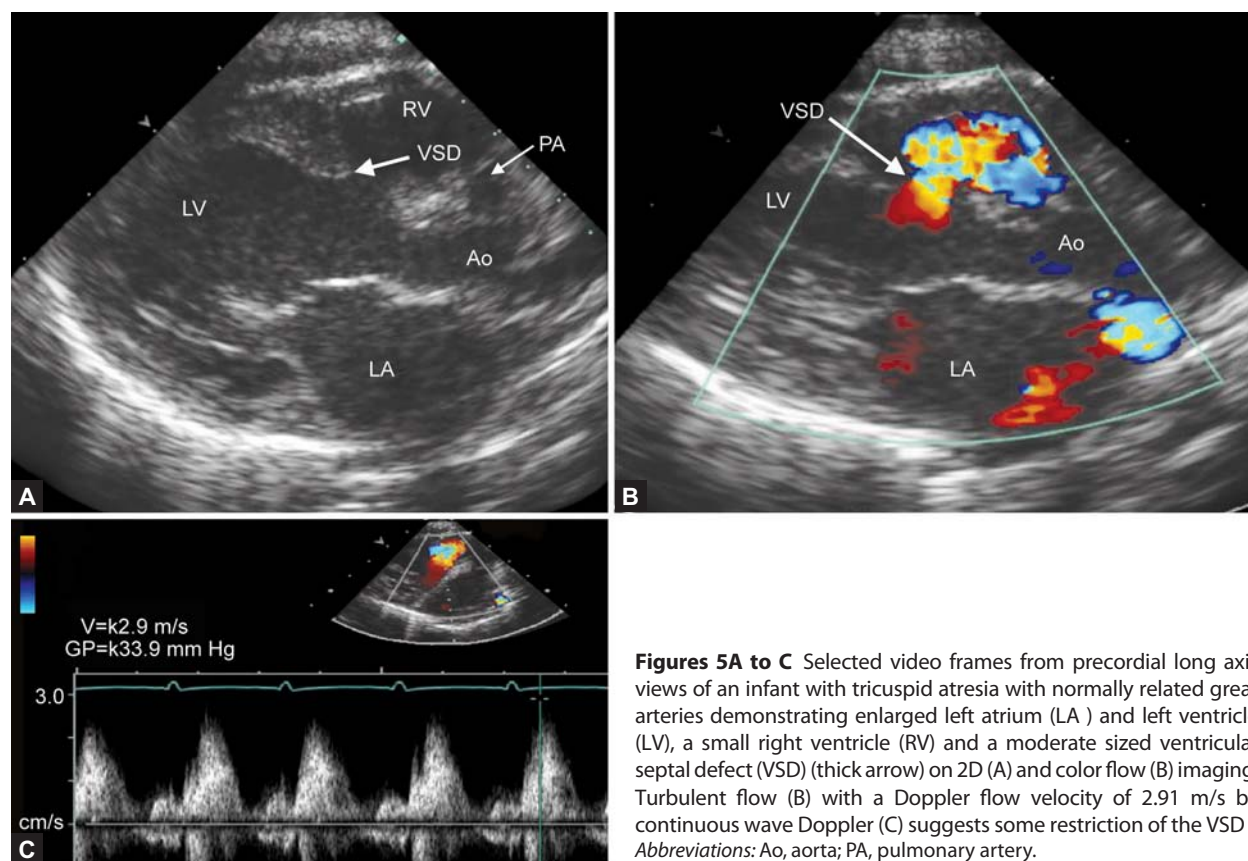
The most frequent defects in this group in the early neonatal period are transposition of the great arteries (TGA), hypoplastic left heart syndrome (HLHS) and coarctation of the aorta syndrome. Patients with multiple left to right shunt lesions manifest more commonly beyond the neonatal period.

Children with TGA typically manifest with severe cyanosis, have minimal distress and have no symptoms of heart failure. Chest X-ray shows mild cardiomegaly with increased pulmonary vascular markings. ECG is either normal or may demonstrate RVH. Blood gases shows severely decreased PO_2 and oxygen saturation. The PO_2 does not get better with 100% O_2 .

Neonates with HLHS show signs of severe congestive heart failure, have minimal cyanosis, but have obvious respiratory distress, hepatomegaly, and decreased pulses in all four extremities.



Figures 4A and B A selected video frame from precordial long axis views of a child with tricuspid atresia and transposition of the great arteries demonstrating left atrium (LA), left ventricle (LV), a very small right ventricle (RV) and a moderate sized ventricular septal defect (VSD). The vessel coming off of the LV is traced in B and shown to bifurcate into left (LPA) and right (RPA) pulmonary arteries confirming that this vessel is main pulmonary artery (MPA)
Abbreviation: Ao, aorta.



Figures 6A and B Selected video frames from suprasternal notch views of the aortic (Ao) arch in 2D (A) and color flow (B) images of a neonate with tricuspid atresia and transposition of the great arteries demonstrating coarctation of the aorta (CoA) and hypoplastic transverse aortic arch (TAA). Abbreviation: DAo, descending aorta.

On chest roentgenogram severe cardiomegaly is present. ECG shows decreased left ventricular forces and RVH. On blood gas analysis, PO_2 and oxygen saturation are only mildly decreased, but may show metabolic acidosis. The PO_2 may improve to some extent

with 100% O_2 , but never above 150 torr. The clinical distinction between TGA, HLHS is rather simple: the main difficulty of infants with TGA is one of cyanosis, whereas the problem of infants with HLHS is one of heart failure with hardly recognizable cyanosis.

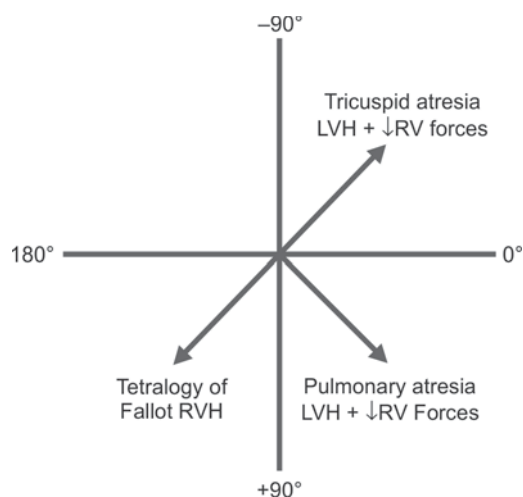


Figure 7 This figure illustrates the usefulness of frontal plane mean QRS vector (axis) in helping differential diagnosis of cyanotic heart defects with decreased pulmonary flow. A frontal plane axis between 0° and -90° is suggestive of tricuspid atresia, an axis between 0° and +90° is indicative of pulmonary atresia with intact ventricular septum and an axis between +90° and ±180° is associated with tetralogy of Fallot. The accompanying ECG abnormalities are also displayed in the appropriate quadrant. Cyanotic infants with complex heart defects with associated severe pulmonary stenosis/atresia may fall into any quadrant

Abbreviations: LVH, left ventricular hypertrophy; RV, right ventricle; RVH, right ventricular hypertrophy.

Babies with coarctation of the aorta may have decreased femoral pulses, are not usually cyanotic, and when low, improve with 100% O₂. Children with TA babies have LAD and LVH on the ECG. Echocardiogram is diagnostic for each of these entities.

When the neonate presents late in the neonatal period, the differential diagnosis is multiple left to right shunts and several complex cyanotic congenital heart defects such as double-in-let left ventricle (Single ventricle), double outlet right ventricle along with tricuspid atresia with a large ventricular septal defect, all without pulmonary stenosis. Majority of defects require echocardiography for making a diagnosis.

MANAGEMENT

Fontan procedure, considered a physiologically “corrective” surgery for TA, is usually performed in patients older than 2 years. However, the majority of children with TA present early in life. Consequently, such early presenting infants must get effective palliation to allow them to reach the age when safe corrective surgery can be undertaken.

1. Medical Management at the Time of Presentation

Management steps during the process of identification, transfer to a pediatric cardiology center, initial workup and during and after palliative surgery or procedures entail preservation of neutral thermal environment, normal acid-base balance and normal blood glucose and calcium with appropriate monitoring and correction, as necessary. Unless there is pulmonary parenchymal pathology, no more than 40% oxygen (FiO₂) is necessary.

Prostaglandin Infusion for Ductal Patency

Neonates with low arterial oxygen saturation are likely to have ductus-dependent pulmonary blood flow. Therefore, the

ductus should be kept open by intravenous administration of prostaglandin E₁ (PGE₁), with a starting dose of 0.05 µg/kg/min and gradually reducing it to 0.02 µg/kg/min, provided the desired oxygen tension levels are maintained. Such low doses are helpful in reducing the frequency and severity of some of the drug’s side effects such as apnea and hyperpyrexia.

Those infants presenting with signs of CHF (more common in type II patients) need treatment with routine anticongestive measures. Neonates with severe coarctation of the aorta also need PGE₁ infusion; this time, the ductal dilating effect of PGE₁ improves systemic perfusion.

2. Palliative Treatment of Specific Physiologic Abnormalities

The functional type of hemodynamic abnormality produced by the cardiac anomalies determines the nature of palliative management. These will be grouped into those with decreased pulmonary blood flow, increased pulmonary blood flow, and intracardiac obstruction.

Decreased Pulmonary Blood Flow

Systemic-pulmonary artery shunts are most commonly used in palliating pulmonary oligemia. Modified Blalock-Taussig shunt, with a Gore-Tex graft interposed between the subclavian artery and the ipsilateral pulmonary artery is most commonly utilized at the present time (Fig. 8). Stenting the ductus arteriosus is not currently an initial therapeutic choice.

Rarely, the predominant obstruction may be at the pulmonary valve level, and in such babies, balloon pulmonary valvuloplasty may help increase pulmonary blood flow.

Increased Pulmonary Blood Flow

Infants with mild to moderate increase in pulmonary blood flow without signs of congestive heart failure should be observed and no treatment is necessary. Infants with markedly increased pulmonary blood flow are likely to develop congestive heart failure; most of these babies belong to type IIc and rarely, type Ic.

In type I babies, anticongestive measures such as diuretics (Furosemide), after load reducing agents (Captopril) and inotropes (Digoxin), as appropriate should be promptly started. The natural history studies show that the VSD spontaneously closes and the

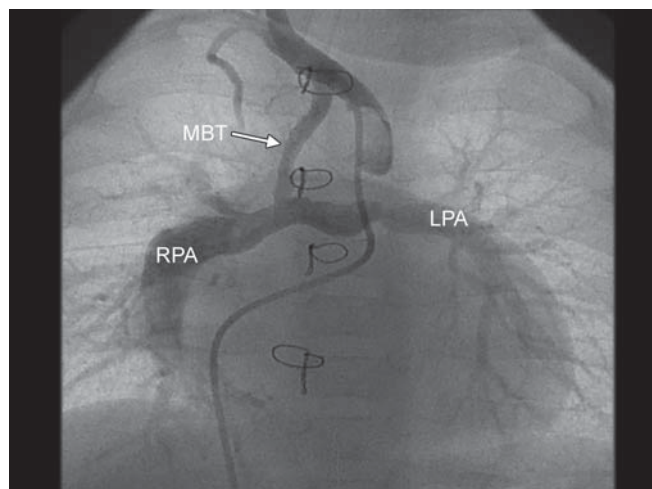


Figure 8 A selected cineangiographic frame to demonstrate a modified Blalock-Taussig (MBT) shunt, connecting the subclavian artery to the right pulmonary artery (RPA) with a Gore-Tex graft (MBT) Abbreviation: LPA, left pulmonary artery.

infants with pulmonary plethora will, in time, develop pulmonary oligemia requiring a palliative shunt. Consequently, the previously resorted to pulmonary artery banding procedure is not performed initially in this group of patients. If optimal anticongestive measures do not result in improvement, then pulmonary artery banding using absorbable band should be entertained.

If pulmonary artery banding is not performed, periodic estimation of pulmonary artery pressure should be undertaken in order to prevent pulmonary vascular obstructive disease. Initially, the absorbable polydioxanone band decreases pulmonary artery pressure by restricting the pulmonary blood flow and helps improve symptoms of heart failure. As the VSD spontaneously closes, the pulmonary artery band is resorbed and prevents severe pulmonary oligemia that may be seen with a conventional non-absorbable band.

In type II babies, banding of the pulmonary artery (**Fig. 9**) should be performed once the infant gets stabilized following anticongestive therapy. If coarctation of the aorta is present, adequate relief of the aortic obstruction should be undertaken concurrent with pulmonary artery banding. The importance of initial PGE₁ administration in the control of congestive heart failure has already been mentioned.

Intracardiac Obstruction

Intracardiac obstruction may develop at the patent foramen ovale and/or at the VSD. The development of interatrial obstruction in a few patients at the patent foramen ovale evidenced by a mean atrial pressure difference of 5 mm Hg or more with prominent 'a' waves (15–20 mm Hg) in the right atrium should be relieved by Rashkind balloon atrial septostomy. Interventricular obstruction with spontaneous closure of the VSD causes severe pulmonary oligemia in type I patients and subaortic obstruction in type II patients.

Management in Type I TA

Cyanotic spells, similar to those observed in tetralogy of Fallot resulting from the functional closures occurring in infants with normally related great arteries (type I), are managed the same way as Fallot's tetralogy spells get treated. Pulmonary oligemia following partial or complete anatomic closure of the VSD in type I patients is treated with Blalock-Taussig shunt in young infants and bidirectional Glenn procedure in older infants and children, preparatory to a modified Fontan operation.

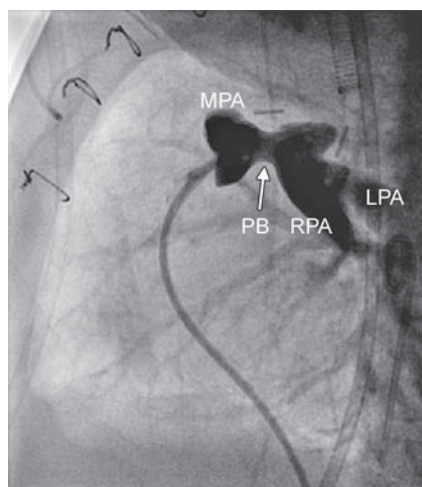


Figure 9 A selected cine frame from main pulmonary artery (MPA) cineangiogram in straight lateral view demonstrating constriction of the pulmonary artery (PB) (arrow)
Abbreviations: LPA, left pulmonary artery; RPA, right pulmonary artery.

Management in Type II (TA with Transposition)

Subaortic obstruction due to partial closure of the VSD in these children is relieved by resection of the conal muscular septum, thereby enlarging the VSD or bypassed by performing anastomosis of the proximal stump of the divided pulmonary artery to the ascending aorta at the time of bidirectional Glenn (or Fontan) operation (Damus-Kaye-Stansel procedure).

3. Medical Management after Palliative Operation

In babies with single ventricle physiology (including palliated tricuspid atresia patients), the systemic and pulmonary circulations function in-parallel rather than normal in-series circuits; a delicate balance of the blood flows between the two circulations exists. Intercurrent illnesses that produce dehydration, acidosis, or fever upset the balance between the two circulations and cause a patient to become critically ill. These intercurrent illnesses do cause significant interstage mortality. In addition blockage of the Blalock-Taussig shunt may develop. Consequently, even minor illnesses must be treated aggressively.

Other issues in TA being similar to those seen in other types of cyanotic heart defects must be closely monitored, prevented whenever possible and treated adequately at the earliest: Relative anemia, polycythemia, coagulopathy, cerebrovascular accident or brain abscess and hyperuricemia, gout, and uric acid nephropathy should be prevented by timely palliative or corrective operative therapy. Antibiotic prophylaxis prior to any bacteremia-producing procedures or surgery is indicated, as is routine immunization plus consideration for palivizumab (for prevention of RSV infection in infancy), polyvalent pneumococcal vaccine or influenza vaccine.

4. Corrective Surgery

Successive modifications of the initially performed Fontan and associates' physiologically corrective surgical procedure for tricuspid atresia have tried to minimize the mortality and the earlier postoperative problems and thus maximize the quality of life of survivors. At the present time staged total cavopulmonary diversion (de Leval and his colleagues) is the procedure of choice because of technical simplicity, maintenance of low right atrial and coronary sinus pressure, and reduction in risk of formation of thrombus in the Fontan circuit.

Stage I

At this stage (**Figs 8 and 9**), usually at presentation in the neonatal period, Blalock-Taussig shunt, observation without any surgery or banding of the pulmonary artery is performed depending upon the status of the pulmonary blood flow as detailed above in the section on "Palliative Treatment of Specific Physiologic Abnormalities".

Stage II

In this stage, a bidirectional Glenn procedure (**Fig. 10**) is performed around the age of 6 months. The bidirectional Glenn procedure consists of anastomosing upper end of the divided superior vena cava, end to side, to the superior aspect of the undivided right pulmonary artery, thus diverting the superior vena caval blood into both right and left pulmonary arteries. Atrial septal defect is also enlarged at this time. The hemodynamic advantages associated with the bidirectional Glenn are improved effective pulmonary flow, reduced total pulmonary flow, and less left ventricular volume overloading. If both right and left superior vena cava are present, bilateral bidirectional Glenn shunting should be performed, especially if the bridging innominate vein is absent or small.

Stage III

Stage III consists of diverting the inferior vena caval blood into the pulmonary artery (**Fig. 11**), usually by an extracardiac, non-

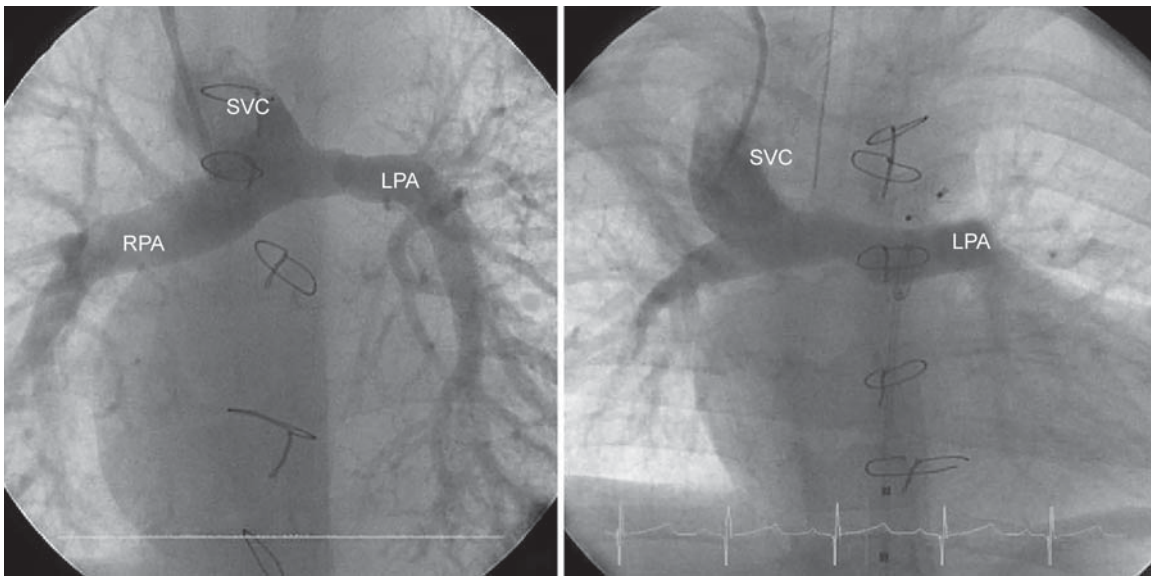
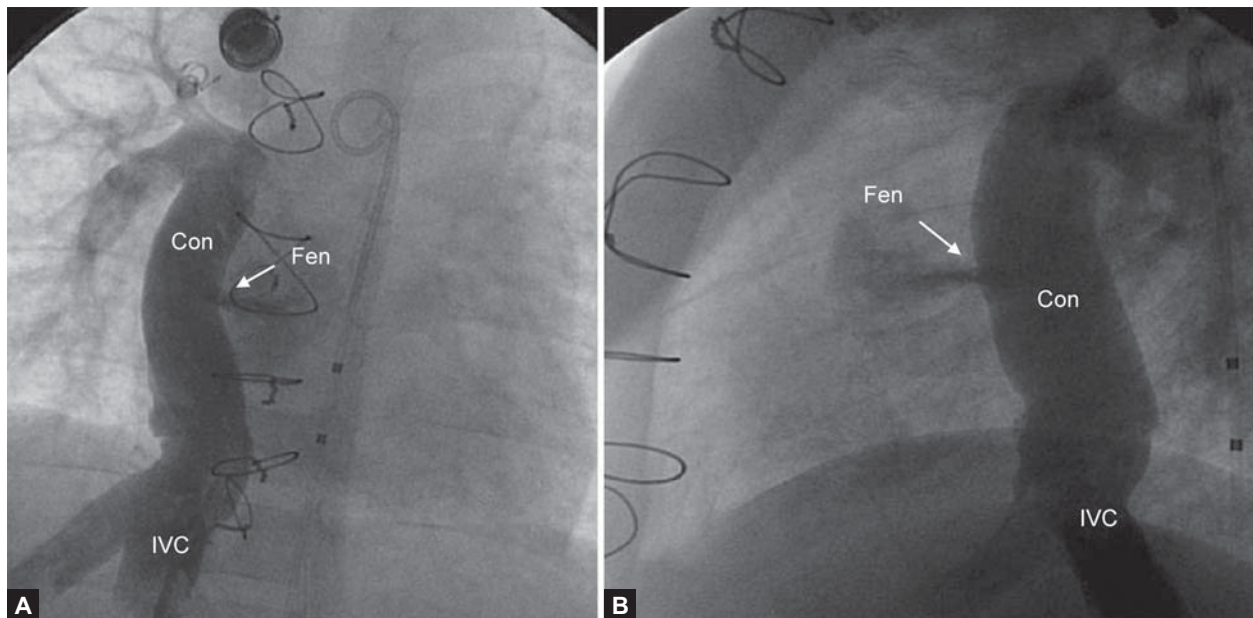


Figure 10 Selected cine frames from superior vena caval (SVC) angiogram in two different children demonstrating the opacification right (RPA) and left (LPA) pulmonary arteries



Figures 11A and B Selected cine frames from inferior vena caval (IVC) angiogram in posteroanterior (A) and straight lateral (B) views demonstrating the conduit (Con) and the fenestration (Fen)

valved conduit (instead of lateral tunnel). Most surgeons leave a fenestration (**Fig. 11**) between the conduit and the right atrium. The procedure is usually performed around the age of 2 years. The fenestration may be closed 6–12 months after Fontan (**Fig. 12**).

Other associated problems such as aortic coarctation, atrial septal obstruction, subaortic obstruction, mitral regurgitation, narrowed pulmonary arteries and others are addressed as and when they are recognized and in association any of the above stages.

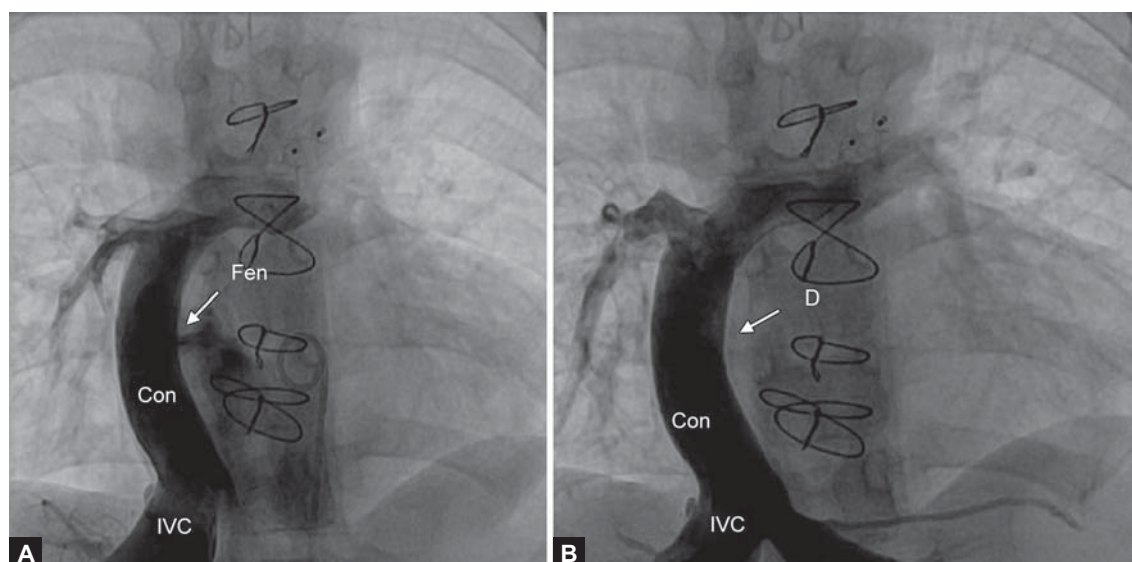
5. Follow-up after Corrective Operation

Continued inotropic and diuretic therapy may be needed in some. Afterload reduction with an angiotensin-converting enzyme inhibitor is advocated whenever needed. Routine use of anticoagulants to prevent development of thrombi in the Fontan

circuit, platelet-inhibiting doses of aspirin is preferred instead of Warfarin. This may be changed to clopidogrel in adulthood. Appropriate monitoring and prompt institution of treatment of complications such as arrhythmia, obstructed pulmonary outflow pathways, persistent shunts, and systemic venous congestion including protein-losing enteropathy.

OUTCOMES/PROGNOSTIC FACTORS

The prognosis of neonates with untreated tricuspid atresia is dismal. Early identification, rapid transport to a center equipped to treat complex congenital heart defects, noninvasive echocardiographic diagnosis, availability of PGE1 to keep the ductus patent, and advances in anesthesia and surgical technique have improved the prognosis of tricuspid atresia babies.



Figures 12A and B Selected cine frames from inferior vena caval (IVC) angiograms in posteroanterior view prior to (A) and immediately following (B) Amplatzer device (D) closure of the fenestration (Fen); note complete closure of the fenestration. The right atrial component of the device (D) is only faintly seen

Abbreviation: Con, conduit.

The next mortality used to be in the second decade of life, which is now reduced with a timely physiologically corrective, Fontan operation. The complications seen with the classic Fontan operation (atriopulmonary anastomosis) such as arrhythmia, atrial thrombosis and protein-losing enteropathy appear to have decreased with current surgical strategy of staged, fenestrated cavopulmonary connection.

PREVENTION

Since a multifactorial inheritance hypothesis is offered to explain all other congenital heart defects, including tricuspid atresia, prevention of the fetus to exposure of environmental triggers is likely to be helpful in prevention; however, no specific factors are clearly identified for tricuspid atresia.

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IN A NUTSHELL

1. Tricuspid atresia (TA) is the third most common cyanotic congenital heart defect.
2. Tricuspid atresia is classified based on the great artery relationship and the status of the pulmonary outflow tract.
3. Tricuspid atresia infants become symptomatic early and 80% of them present with symptoms within the first month of life.
4. Presence of LAD in ECG in a cyanotic infant is characteristic and virtually diagnostic of TA.
6. Prompt diagnosis and treatment to normalize pulmonary blood flow by PGE₁ administration and Blalock-Taussig for babies with pulmonary oligemia and anticongestive measures and banding of the pulmonary artery for infants with pulmonary plethora are likely to improve prognosis.
7. Staged cavopulmonary anastomosis is the treatment of choice for tricuspid atresia.

Chapter 40.23

Transposition of Great Arteries

R Suresh Kumar, Navaneetha Sasikumar

Transposition of great arteries (TGA) is a condition in which the great arteries arise from the wrong ventricles—aorta from right ventricle (RV) and pulmonary artery (PA) from left ventricle (LV). The term complete TGA refers to the condition in which there is ventriculoarterial discordance (as indicated above) with atrioventricular concordance (right atrium to RV and left atrium to LV) and indicates that the transposition is not physiologically corrected. This may occur in situs solitus or situs inversus. Corrected TGA refers to the state where there is both ventriculoarterial and atrioventricular discordance (RA-LV-PA and LA-RV-Aorta) thereby resulting in physiologically corrected circulation.

EPIDEMIOLOGY

Complete TGA, accounting for 5–7% of all congenital cardiac malformations, is the most common cardiac cause for cyanosis in the newborn. Males are more frequently affected than females, with a reported male: female ratio ranging from 1.5:1 to 3.2:1. Non-cardiac malformations are uncommon and are found only in less than 10% of cases.

ETIOPATHOGENESIS

As with most of the other congenital cardiac malformations, the exact etiology is not known. Though not universally accepted, gestational diabetes mellitus and prenatal exposure to sex hormone therapy have been reported to be risk factors associated with occurrence of TGA.

In complete TGA, the atria are connected to the appropriate ventricles (atrioventricular concordance), but there is inappropriate origin of the great arteries from ventricles (ventriculoarterial discordance). Embryologically, the origin of PA from RV depends on the development of the subpulmonary infundibulum, which pushes the pulmonary valve upwards and anteriorly. In TGA, the infundibulum develops under the aortic valve, pushing it up and anteriorly to connect to the anterior RV. Absence of the subpulmonary infundibulum causes the pulmonary valve to stay posterior and connect to the posterior LV. The most common spatial orientation of the aortic valve is to the right and anterior to the pulmonary valve (D-transposition), though there may be other variations. Coronary arteries originate from the aortic sinuses facing the pulmonary trunk, but the pattern of distribution varies. Understanding of coronary artery anatomy is of extreme importance to the operating surgeon while performing the arterial switch operation.

Nearly 50% of cases of TGA have associated patent foramen ovale or patent ductus arteriosus. Ventricular septal defect (VSD), left ventricular outflow tract (LVOT) obstruction—amounting to pulmonary stenosis and aortic arch anomalies (coarctation of aorta or interrupted aortic arch) are the other common associations.

HEMODYNAMICS

The hemodynamics of complete TGA with intact ventricular septum [with or without an atrial septal defect (ASD)/patent ductus arteriosus (PDA)] differs from complete TGA with a VSD and/or left ventricular outflow tract obstruction. The latter two will be discussed separately.

In contrast to the normal circulation in series, the circulation in hearts with complete TGA with intact ventricular septum is parallel.

There are two closed circuits. In the first circuit, oxygenated blood flows from the lungs to the left heart only to get pumped back into the pulmonary circulation (through the pulmonary artery arising from the left ventricle). In the parallel second circuit, deoxygenated blood from the right heart chambers is pumped into the systemic circulation (through the aorta arising from the right ventricle) and returns back to the right side. Survival is possible only if there is adequate mixing between the two circulations. Adequacy of inter circulatory mixing is dictated by the location and size of communications, further modified by the pressure gradients and vascular resistances in the respective circuits.

The anatomy and physiology of complete TGA does not affect normal fetal growth and development significantly. Hence, the newborn with TGA has normal weight or may be even heavier. Hypoxia sets in soon after birth. During the brief transitional period, the PDA shunts deoxygenated blood from aorta to the pulmonary artery (effective pulmonary blood flow) and the patent foramen ovale (PFO) shunts oxygenated blood to the right side of the heart and ultimately into aorta (effective systemic blood flow). This intercirculatory mixing may at times be enough to prevent severe hypoxemia. In most of the newborns, the ductus begins to close, resulting in severe hypoxemia, just as the oxygen demand is increasing due to increased metabolism. This leads to increased anaerobic metabolism, increased lactate production and severe metabolic acidosis. The ductus provides systemic venous flow into the PA and the left atrial volume overload drives left to right shunt across PFO, thus delivering some oxygenated blood into aorta and improving systemic oxygen saturation. This forms the basis of prostaglandin E1 infusion in newborns with complete TGA.

When a large VSD is present effective mixing between the two circulations results in minimal cyanosis. Instead, these infants develop cardiac failure by 2 to 6 weeks of life. Complete TGA with a large VSD is prone to accelerated development of pulmonary vascular disease. As definitive treatment is not possible with the development of pulmonary vascular obstructive disease, these infants need early and timely diagnosis and corrective surgery.

Left ventricular outflow tract obstruction occurs in 30% of cases with TGA and VSD; the anatomic substrate is usually complex and occurs at multiple levels. When VSD coexists with LVOT obstruction (pulmonary stenosis) in a patient with TGA, hemodynamics depends on the size of the VSD and the severity of the pulmonary stenosis. When VSD is large and LVOT obstruction severe, the pathophysiology and clinical presentation resemble that of tetralogy of Fallot (TOF).

CLINICAL FEATURES

TGA with Intact Ventricular Septum

These neonates present from day one of life with cyanosis. The first sound is normal, and the second heart sound is single, as the posterior pulmonary valve closure is inaudible. Usually there is no murmur. As the ductus closes, these patients present with worsening cyanosis and tachypnea.

Arterial blood gases show severe hypoxemia and metabolic acidosis. Cyanosis in TGA is uniform. However, reverse differential cyanosis with upper limbs more cyanosed than the lower limbs may be seen if complete TGA is associated with coarctation and a PDA shunting from PA to aorta.

TGA with Large Ventricular Septal Defect

Mild cyanosis might be noticed in the early neonatal period, which becomes more prominent during crying. Physical examination during this period is unremarkable. As the pulmonary vascular resistance falls, the neonate develops clinical features of cardiac failure by 2–6 weeks of life—rapid breathing, feeding difficulty

(suck-rest-suck cycle) and excessive sweating. On examination, cyanosis is usually mild. Resting tachycardia and tachypnea are present and there is increased precordial activity. A third heart sound and low-frequency mid-diastolic flow murmur may be heard at the apex. An early systolic murmur may be heard at the left lower sternal border, the murmur is louder and longer, if the VSD is restrictive. Crepitations in the lung fields and tender hepatomegaly may be the other findings in these neonates with cardiac failure.

TGA with Ventricular Septal Defect and Pulmonary Stenosis (TGA, VSD with PS)

The clinical features of these patients are often indistinguishable from those with tetralogy of Fallot, although cyanosis tends to appear earlier and is more severe. If the pulmonary stenosis is severe, the baby presents with severe cyanosis once the ductus closes. If this is not the case, cyanosis gradually increases with passage of time and later hypoxic spells may occur. Squatting for relief of dyspnea might be noted in older children. There are no features of cardiac failure. The second heart sound is single. A harsh, ejection systolic murmur, arising from flow across the left ventricular outflow tract is present. If the ductus arteriosus is patent, a continuous murmur may be heard below the left clavicle.

APPROACH TO DIAGNOSIS

The most common cyanotic congenital heart disease in newborns on day one is complete TGA, the major differential diagnosis being TOF with severe right ventricular outflow tract obstruction. Presence of a murmur and reduced lung vascularity on chest X-ray indicates TOF. When the neonate presents with profound cyanosis around 48–72 hours of life, coinciding with the timing of ductal closure, other conditions with duct dependent pulmonary circulation should be excluded, e.g., critical pulmonary stenosis or pulmonary atresia with intact ventricular septum. When a large VSD is present and the neonate presents with cardiac failure, the clinical picture mimics other CHDs with increased pulmonary blood flow.

DIAGNOSIS

ECG and chest X-ray findings of the three variants described above are summarized in **Table 1**.

Echocardiography

Echocardiography is the investigation of choice to establish the diagnosis of TGA and to guide the management strategy. Systematic segmental approach, using a combination of imaging windows (subcostal, apical, parasternal and suprasternal) helps in demonstrating atrioventricular concordance and ventriculo-arterial discordance which is characteristic of complete TGA (**Fig. 1**). Associated defects like VSD, ASD, PDA, LVOT/arch obstruction must be looked for. The spatial relationship of the aorta

to the pulmonary artery as well as the coronary anatomy can also be clearly delineated on echocardiography (**Fig. 2**).

Fetal echocardiography can identify TGA in utero. In utero diagnosis facilitates delivery in a tertiary care center where prostaglandin E₁ (PGE₁) therapy can be started and further cardiac care can be provided before severe hypoxia and acidosis set in.

Cardiac Catheterization

Currently, cardiac catheterization is indicated only for neonates requiring a balloon atrial septostomy. Similar systolic pressures are noted in RV and aorta, while left ventricular and pulmonary artery pressures are lower. Left atrial mean pressure is higher before balloon atrial septostomy and drops after that. Systemic arterial PO₂ may be as low as 15–20 mm Hg with saturations like 40–50%. Right ventricular angiogram will show aorta arising from the RV. Older children may need catheterization as part of presurgical evaluation especially in those with VSD and PS, or for evaluation of the severity of pulmonary vascular obstructive disease, if present.

MANAGEMENT

It is important to stabilize the critically ill hypoxic neonate before referring for definitive management. This includes attention to common neonatal issues—correction of hypothermia, hypoglycemia, acidosis, hypocalcemia, dehydration and treatment of sepsis, if any. These problems must be attended to, while investigations are being done. Some neonates may require endotracheal intubation and mechanical ventilation.

Prostaglandin E1 Infusion

It has a major role in stabilizing the neonate with TGA and severe hypoxia. The drug is started as an infusion at an average dose of 50 ng/kg/min (range 10–100 ng/kg/min). The SpO₂ improves to at least 70% in most of these neonates who are only a few days old. Using the lowest effective dose helps to minimize tachycardia and to avoid apnea. PGE₁ infusion increases safety of transportation.

Balloon Atrial Septostomy (BAS)

BAS is a temporizing measure to improve systemic oxygen saturation in the severely hypoxic neonate. First performed by Rashkind in 1966, it marked the beginning of interventional pediatric cardiology. This is indicated in the newborn with TGA/intact IVS and inadequate atrial mixing. It may not be required if unless arterial switch operation is planned in the first week. A balloon catheter is introduced across a PFO from the femoral or umbilical vein. It is filled with contrast material and is pulled across the interatrial septum, under fluoroscopic or echocardiographic guidance, tearing the septum and creating an adequate interatrial communication for intercirculatory mixing. BAS results in immediate improvement of SpO₂ to about 70% and may further rise to 80–90%, if it is combined with PGE₁ infusion.

Table 1 ECG and radiological findings in TGA

	<i>Complete TGA with intact ventricular septum</i>	<i>Complete TGA with large VSD</i>	<i>Complete TGA with VSD and left ventricular outflow tract obstruction</i>
ECG	Right axis deviation (RAD) and right ventricular hypertrophy (RVH) Upright T in V1	Biventricular hypertrophy (BVH), RAD LV volume load	RVH, RAD
Chest X-ray	Egg-on-side cardiac shadow with narrow superior mediastinum; Mild cardiomegaly; Increased pulmonary vascular markings	Cardiomegaly with prominent pulmonary vascular marking; Superior mediastinum is narrow	Decreased pulmonary vascular markings; Normal heart size

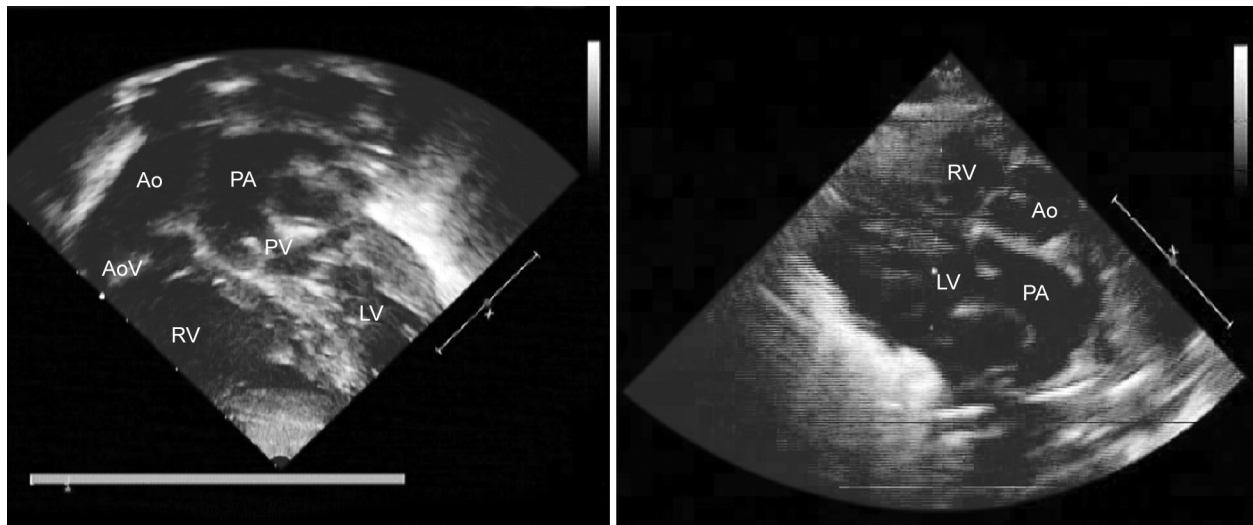


Figure 1 Subcostal (left) and parasternal long axis views (right) showing the great arteries arising from the “wrong” ventricles

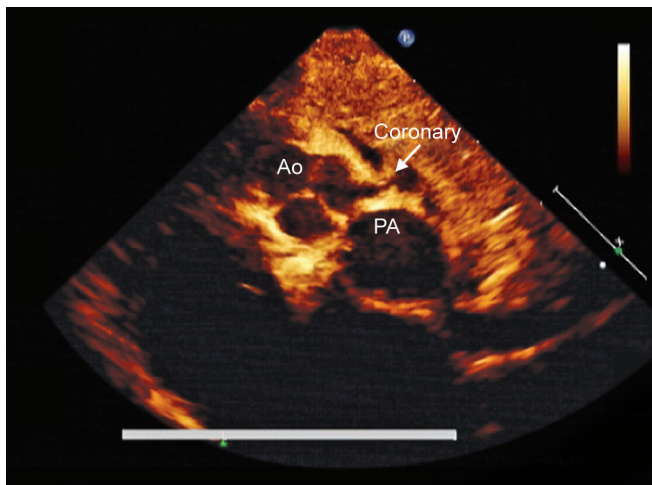


Figure 2 2-D echocardiogram in complete transposition. Parasternal short axis view showing aorta right and anterior to pulmonary artery. Note the coronary arteries arising from the facing sinuses

Arterial Switch Operation (ASO)

It is today the standard of care of infants with complete TGA. Initially performed by Jatene, the surgery involves transection of aorta and PA so as to cross connect their proximal and distal ends, coronary artery translocation to the new aortic root, and pulling the pulmonary arteries anterior to aorta (Le Compte maneuver). The surgery needs to be undertaken in the first month of life as the LV regresses fast and becomes less efficient in pumping against the systemic circulation. Most surgical centers perform this surgery with less than 5% mortality and excellent long-term outcome.

Management of Late Presenters

The infant with TGA presenting after the first month of life presents a unique challenge in the developing world. Careful assessment of left ventricular adequacy is required. Left ventricular posterior wall thickness, sphericity, mass index and

its relation to left ventricular volume all figure prominently in deciding the suitability for arterial switch operation. The infant unsuitable for primary arterial switch operation may undergo pulmonary arterial banding to prepare the left ventricle to cope up with the increased workload, followed by arterial switch operation after a few weeks to few months (2-stage arterial switch). The alternative is a Mustard (Dacron baffle) or Senning (no synthetic material) operation, where pulmonary venous blood is baffled within the atrium to tricuspid valve and systemic venous return to mitral valve so that RV is allowed to be the systemic ventricle. The strategy gives good results for 10–20 years, after which arrhythmias and systemic ventricular dysfunction become major problems.

TGA with VSD

These infants present with heart failure by 4–6 weeks. They have a tendency to develop pulmonary vascular disease after 3 months of age. Arterial switch operation (and VSD closure) must be undertaken before 3 months to prevent this.

TGA with VSD and LVOT Obstruction (Pulmonary Stenosis)

The presentation depends on the severity of LVOT obstruction, which determines the degree of hypoxia. Severe LVOT obstruction warrants a modified Blalock-Taussig shunt for palliation in early infancy. Less hypoxic infants are followed up with plan for definitive correction by 3–5 years. The definitive procedure is Rastelli operation-baffling the left ventricle to aorta by VSD closure and connecting RV to PA with a conduit. With current technology such children require conduit change several times in their life time.

OUTCOME

If left untreated, 30% of infants with TGA and intact interventricular septum die in the first week of life, 50% within the first month, 70% within six months, and 90% within the first year. Given a large VSD or PDA, survival into first or second decade may occur, but pulmonary vascular disease is almost invariable. Infants with TGA with associated VSD and pulmonary stenosis, when optimally balanced, have longer survival as seen in infants with TOF.

Ten year survival rates of 85–90% have been reported for atrial switch surgeries—Mustard/Senning. Although survival into third or fourth decade may be expected, there is increasing morbidity after the first decade from arrhythmias (sinus node dysfunction), systemic ventricular failure, baffle obstructions and leaks.

Following arterial switch operation done in 1982–99, Losay et al. reported early mortality of 9.2% and survival of 88% at 10 and 15 years. Significant supraaortic pulmonary stenosis and/or neoaortic regurgitation was present in 9%, the former being the most common cause for redo surgery. LV function was well preserved and arrhythmias were uncommon. Asymptomatic coronary artery occlusion may be seen in some.

More recent series report mortality below 5%. Long-term neurodevelopmental outcome in these children is a matter of keen interest, as some manifest problems years later. Conduit obstruction, left ventricular outflow tract obstruction, and arrhythmias contribute to late morbidity and mortality.

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IN A NUTSHELL

1. TGA is the most common cardiac cause for neonatal cyanosis.
2. Profound hypoxemia, no murmur, increased lung vascularity and egg-on-side cardiac silhouette are clinical clues to the diagnosis of TGA.
3. 2-D echocardiography is the gold standard for diagnosis.
4. Prostaglandin infusion can help in stabilizing a severely hypoxic neonate, before transferring to a tertiary care center.
5. Balloon atrial septostomy (BAS) is performed, if arterial switch operation is not being done immediately. BAS significantly improves SpO₂ and usually allows the baby to stay with the mother.
6. Arterial switch operation, done in the first month of life is the benchmark of present day care in TGA. In good centers this surgery carries less than 5% mortality.
7. Long-term neurodevelopmental outcome needs close monitoring after neonatal arterial switch.
8. In utero diagnosis by fetal echocardiography helps in better planning of neonatal management.

Chapter 40.24

Truncus Arteriosus

Duraisamy Balaguru

Truncus arteriosus (T.Art) is a conotruncal anomaly characterized by a common arterial trunk from which pulmonary artery (PA) originates. T.Art is a distinct entity from aortopulmonary window where the great arteries have a communication between them and there are two separate semilunar valves.

PATHOLOGY AND CLASSIFICATION

Truncus arteriosus is characterized by presence of only one semilunar valve (truncal valve) from which a common arterial trunk originates. The PAs originate from the ascending portion of the common arterial trunk either as main PA which then bifurcates or as separate branch PA and the pattern of origin of PAs is the basis for Collett and Edward's Classification (1949) (**Fig. 1**). Type 4 shown is no longer considered part of T.Art and is reclassified under pulmonary atresia with ventricular septal defect.

Associated Lesions

A typically large and malaligned ventricular septal defect (VSD) is invariably present with rare exceptions. Truncal valve is sometimes quadricuspid (24%). Other lesions include right sided aortic arch (16%), interrupted aortic arch (10%), atrial septal defect (10%), mitral valve hypoplasia (10%), persistent left superior vena cava (6%), additional VSDs (4%), complete atrioventricular septal defect (2%), extracardiac anomalies (10%) and DiGeorge syndrome (33%). When T.Art occurs with right sided aortic arch or interrupted aortic arch, a possible association with DiGeorge syndrome is extremely high (50–84%). Typically, ductus arteriosus is absent in T.Art, except when associated with interrupted aortic arch.

ETIOLOGY

The etiology of T.Art is multifactorial (genetic and environmental). When associated with right aortic arch anomaly, DiGeorge syndrome with chromosomal microdeletion at 22q11.21 is a high possibility. Velocardiofacial syndrome, CATCH22, Shprintzen syndrome and conotruncal anomaly face syndrome are other names associated with this genetic defect. Developmentally, defective migration of cardiogenic neural crest cells that form the conotruncal portion of the heart leads to defective spiral septum

formation, e.g., failure of separation of common arterial trunk into two great arteries.

CLINICAL PRESENTATION

In late neonatal period children with T.Art present with mild, subtle cyanosis that may be missed by even well trained eyes because of increased pulmonary blood flow. They present clinically in the first 3 months with poor and interrupted feeding, respiratory distress, tachypnea, tachycardia, features of heart failure due to fall in the neonatal pulmonary vascular resistance from regression of fetal PA musculature.

If T.Art with interrupted aortic arch is not recognized prior to patent ductus arteriosus (PDA) closure, neonates present when PDA closes in a few days of age with absent femoral pulse, circulatory shock, respiratory distress and metabolic acidosis. Without interrupted aortic arch, presentation depends on presence and degree of PA stenosis.

Physical Examination

As outlined above, physical findings are dependent on the status of pulmonary blood flow. In a typical patient without PA stenosis, there are features of increased pulmonary blood flow with diastolic reversal of flow in the aorta. This leads to a large volume pulse with hyperdynamic precordium. Tachypnea, chest retraction with features of heart failure from increased pulmonary blood flow will be notable similar to cases of a large VSD. When there is PA stenosis, pulmonary blood flow is normal or decreased, there will be cyanosis without signs of respiratory distress. Auscultation reveals normal or loud S_1 . Systolic click from truncal valve abnormalities or dilatation of the common arterial trunk may be present. Single S_2 is noted due to presence of only one semilunar valve. Loud S_2 in the presence of pulmonary hypertension in older infants is expected. There will be a systolic ejection murmur from PA stenosis. This may be high pitched, continuous murmur if there is significant stenosis. Truncal valve regurgitation if present will manifest a high-pitched, early diastolic murmur similar to aortic regurgitation. An apical, low-pitched diastolic rumble (mid-diastolic murmur) of increased flow through a normal mitral valve will reflect increased pulmonary blood flow.

DIFFERENTIAL DIAGNOSIS

For infants with cyanosis, differential diagnosis will include the other cyanotic conditions with increased pulmonary blood flow—transposition of great arteries with ventricular septal defect, double-outlet right ventricle, tricuspid atresia with large VSD, single ventricle without pulmonary stenosis and total anomalous

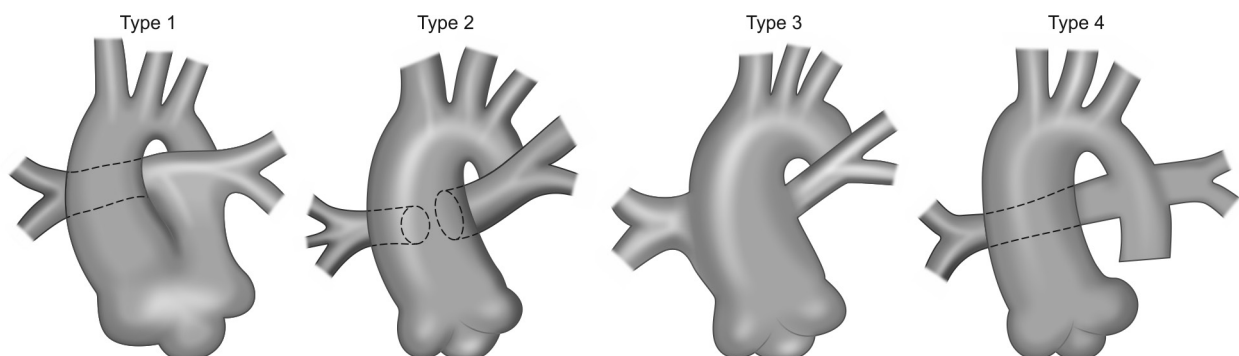


Figure 1 Collett and Edward classification of truncus arteriosus (1949). Note: Type 4 is no longer considered a type of truncus arteriosus, but is considered a type of pulmonary atresia with ventricular septal defect

pulmonary venous return (TAPVR). Tricuspid atresia will have an ECG with left axis deviation and left ventricular dominance. TAPVR will have right ventricular dominance.

NATURAL HISTORY

The survival of infants born with T.Art without any specific intervention is 30% beyond 3 months and only 12% beyond the first year. The cause of death is heart failure from increased pulmonary blood flow and early development of pulmonary arterial hypertension (PAH). Those who survive beyond 1 year have associated PA stenosis that restricts increased pulmonary blood flow and development of PAH. Nearly, half of these survivors live up to their teen age or beyond. Eventually, Eisenmenger syndrome due to severe PAH sets in making it inoperable.

DIAGNOSIS

Chest X-ray

Cardiomegaly in an infant with increased pulmonary vascular markings (**Fig. 2**) arising from the hilar regions in a slightly higher position is typical. Presence of right sided aortic arch in early infancy with previously described clinical features offers a reasonable clue to the likelihood of presence of T.Art. An infant with T.Art and severe PA stenosis will have normal sized cardiac silhouette and normal or diminished pulmonary vascular markings. Cardiomegaly and pulmonary plethora decrease in older children with the development of PAH.

Electrocardiogram

Electrocardiogram findings are not diagnostic. In newborn, initial ECG may be normal for age. Normal axis with biventricular hypertrophy in a minimally cyanotic infant must entertain this diagnosis. Left ventricular hypertrophy alone may be a later finding. Right arterial enlargement is seen in late infancy and childhood with the development of PAH.

Echocardiogram

Echocardiogram, diagnostic of T.Art, is characterized by presence of only one semilunar valve over-riding a malaligned large outlet VSD. Type of T.Art will be recognized from pattern of origin of PA. Other objectives of performing echocardiogram are to define



Figure 2 Chest X-ray of a 5-day-old newborn with truncus arteriosus. Chest X-ray shows moderate cardiomegaly and bilateral increased pulmonary vascular markings with congestion. This is characteristic but not diagnostic of truncus arteriosus

and detect truncal valve anatomy and function, branch PA size and stenosis, sidedness and patency of aortic arch, and other associated defects. Rarely, cardiac MRI or cardiac catheterization are performed, when echocardiogram cannot define all necessary aspects of the defect, especially when aortic arch or its interruption cannot be clearly defined.

TREATMENT

Initial Medical Management

The modes of clinical presentation determine the initial medical management. When the newborn presents due to associated interrupted aortic arch and closure of ductus arteriosus, management consists of resuscitation and stabilization, along with starting prostaglandin infusion to reopen ductus arteriosus. In neonate or young infant with T.Art, who presents with increased pulmonary blood flow and features of heart failure, diuretics and digoxin should be used in adequate doses along with adequate nutrition with daily calorie intake exceeding 100 calories/kg/day. Hypocalcemia and immunodeficiency related to DiGeorge syndrome will need appropriate medical management.

Surgical Management

Surgical repair of T.Art (**Fig. 3**) consists of closure of VSD using a patch, disconnection of PA from common arterial trunk and repair of this site and placement of a valved, homograft conduit (RV-PA conduit) from right ventricle to the disconnected PA. Truncal valve repair may be needed when regurgitation is severe. Timing of surgery depends on the status of pulmonary blood flow. If the baby is asymptomatic, surgery may be performed at any time from birth to 4-6 weeks. Palliative PA banding is no longer favored due to technical difficulties. After neonatal period, surgical repair is done as soon as the condition is diagnosed. T.Art with interrupted aortic arch always warrants neonatal repair in spite of its associated higher risk.

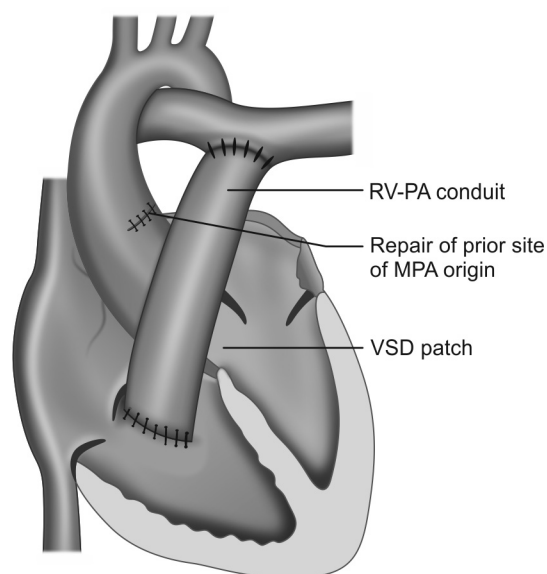


Figure 3 Surgical repair of truncus arteriosus. Repair consists of VSD patch closure, RV-PA conduit using a valved-homograft and repair of the prior site of origin of main pulmonary artery in type 1 truncus (or branch PA in types 2 and 3)

Abbreviations: VSD, ventricular septal defect; MPA, main pulmonary artery; RV-PA conduit, right ventricle to pulmonary artery conduit.

OUTCOME

Early surgical mortality is 10%. Mortality increases to 30% with additional truncal valve repair and to 60% with interrupted aorta repair. In the long-term, these operated children need repeat surgeries to replace RV-PA conduits as the child grows and possible balloon dilatation or stenting of stenosed PA branch by interventional catheterization. Reported survival at 15 years is 83% in the early survivors of initial surgery.

Follow-up

The objectives of much needed regular follow-up of operated patients are to identify long-term sequelae and progression of residual lesions such as stenosis of RV-PA conduit, regurgitation of truncal valve or conduit valve, and branch PA stenosis. Recoarctation may occur in patient who needed repair of interrupted aortic arch. In a stable patient, yearly follow-up with clinical examination, Chest X-ray, ECG and echocardiogram will suffice.

Unoperated patients may need to be evaluated for reversibility of pulmonary hypertension by cardiac catheterization with pulmonary vasoreactivity testing. However, if the patient is inoperable, palliative medical care is indicated. Follow-up evaluation will include recording pulse oximetry for systemic oxygen saturation, symptomatic management of cyanosis and its consequence, and heart failure secondary to pulmonary hypertension.

Long-term Outcome

Natural history section above provides outcome for unoperated patients. Among operated patients who survive early surgery, 83% survival is noted at 15 years of age. These survivors can be expected to have normal growth and development, barring any intraoperative complications such as stroke and developmental delay from DiGeorge syndrome or other extracardiac anomalies.

Maintenance of good dental hygiene and endocarditis prophylaxis are indicated. Even though, they are restricted from competitive sports active lifestyle with recreational sports is encouraged.

IN A NUTSHELL

1. Truncus arteriosus is almost invariably associated with malalignment of VSD.
2. Associated lesions (PA stenosis and interrupted aortic arch) alter the clinical presentation.
3. Truncus arteriosus with right aortic arch has high association with DiGeorge syndrome.
4. Clinical presentation depends on severity of associated lesions.
5. Medical management is only temporizing measure. Surgery is indicated during infancy.
6. Outcome for isolated T.Arch is better than when associated with truncal valve regurgitation or interrupted aortic arch.

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Chapter 40.25

Ebstein Anomaly, Pulmonary Arteriovenous Fistula, Corrected Transposition of Great Arteries

Sunita Maheshwari

EBSTEIN ANOMALY

Ebstein anomaly, seen in 1 per 200,000 livebirths, is an abnormality of the tricuspid valve which can lead to tricuspid regurgitation (TR) and varying degrees of true right ventricular hypoplasia. The functional impairment of the right ventricle (RV) and regurgitation of the tricuspid valve retard forward flow of blood through the right side of the heart. In addition, during contraction of the atrium, the atrialized portion of the RV balloons out, decreasing further the volume of ejected blood. The overall effect on the right atrium is dilation which in turn increases the size of right to left shunting across the atrial septal defect (ASD), if present.

Presentation

Ebstein anomaly can present in the neonate with functional pulmonary atresia due to elevated pulmonary vascular resistance. Signs include respiratory distress, cyanosis and right heart failure, the clue being the presence of massive cardiomegaly (**Fig. 1**) on chest X-ray (CXR) (right atrial enlargement). Alternately, it can be relatively asymptomatic and present later with cyanosis (if there is a concomitant ASD going right to left) or arrhythmias due to the presence of accessory pathways or dyspnea and fatigue due to the TR and cardiomegaly.

The jugular venous pulse (JVP) rarely shows a large V wave despite severe regurgitation of the tricuspid valve because the large right atrium accommodates the increased volume. A widely and persistently split second heart sound and several added sounds are typical. A third and fourth heart sound contribute to the common gallop rhythm. A systolic or diastolic murmur may be audible. Cyanosis and clubbing maybe present.

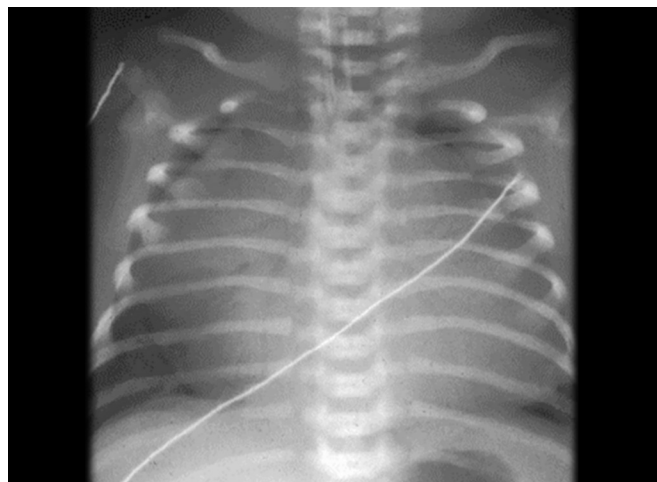


Figure 1 Massive cardiomegaly seen in neonatal Ebstein anomaly

Diagnosis

The ECG is characteristic with *tall* p waves as well as first degree heart block and low amplitude QRS complexes in the right precordial leads (due to the small true RV). An echocardiogram is diagnostic. The main feature is apical displacement of the septal leaflet of the tricuspid valve from the insertion of the anterior leaflet of the mitral valve (**Fig. 2**) by at least 8 mm/m² body surface area.

While Ebstein anomaly is defined as the congenital displacement of the tricuspid valve towards the apex of the right ventricle, it is often associated with other abnormalities such as an ASD or Wolff-Parkinson-White (WPW) syndrome (pre-excitation).

Treatment

Management varies depending on the clinical scenario of each patient. In neonates in extremis due to functional pulmonary atresia, prostaglandins are lifesaving as they keep the ductus arteriosus open allowing pulmonary blood flow. Simultaneously, oxygen is used to drop the pulmonary vascular resistance which helps forward flow across the pulmonary valve. Complex surgery including tricuspid valve repair or if that is not feasible, closure of the tricuspid valve converting the heart into a single ventricle can be attempted.

Asymptomatic children without significant cyanosis or cardiomegaly can be followed. In the older age group, surgery can be performed for the following indications:

- Limited exercise capacity (NYHA class 3–4)
- Increasing heart size (cardiothoracic ratio greater than 65%).
- Significant cyanosis
- Severe TR with symptoms.

Medical treatment includes diuretics for heart failure. Digoxin should be used with care in the presence of WPW syndrome. Surgical options tend to be highly individualized and include tricuspid valve repair or replacement +/- ASD closure. In situations where the RV is too small, a Glenn shunt (superior vena cava to pulmonary artery connection) may be added to offload the ventricle. If arrhythmias are a presenting complaint, radiofrequency ablation of the accessory pathway will need to be added to the treatment armamentarium.

Individuals with mild Ebstein anomaly, near normal heart size, and no arrhythmias can participate in all sports. Children with severe Ebstein anomaly are at risk for sudden cardiac death and are precluded from sports unless the anomaly has been optimally surgically repaired, the heart size is nearly normal, and no history of arrhythmias exists.

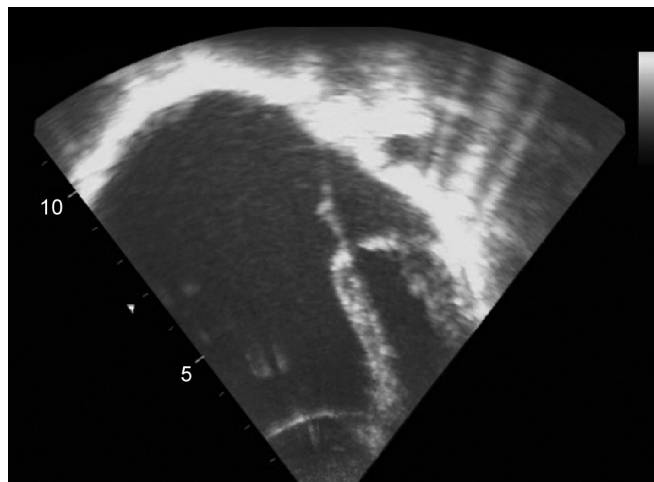


Figure 2 Ebstein anomaly of the tricuspid valve

PULMONARY ARTERIOVENOUS FISTULA

Pulmonary arteriovenous fistula (AVF) is an abnormal connection between an artery and vein in the lungs. Physiologically, the deoxygenated blood from the pulmonary arteries bypasses the capillaries (where oxygenation normally takes place) and directly enters the pulmonary veins and left atrium. So blue blood re-enters the systemic circulation causing cyanosis.

Most commonly pulmonary AVF occur in patients with Osler-Weber-Rendu disease, now commonly called hereditary hemorrhagic telangiectasia (HHT). These patients often have abnormal blood vessels in many parts of the body, including the lung. The 80–90% of patients with pulmonary arteriovenous malformations (AVMs) have HHT. Pulmonary arteriovenous (AV) fistulae can also be seen after certain congenital heart surgeries due to lack of the so called hepatic factor reaching the lungs (e.g., Kawashima, nonpulsatile Glenn). Additionally they can be seen in patients with liver cirrhosis for the same reason.

Presentation

Pulmonary arteriovenous malformations (PAVMs) are classified as *simple* or *complex*. The simple type has a single segmental artery feeding the malformation. Complex malformations have multiple segmental feeding arteries. There is a rare, diffuse form of the disease characterized by hundreds of malformations. Classifying the lesions is helpful in planning treatment, in determining which lesions can be embolized and what form of therapy is most appropriate.

The classical clinical findings are cyanosis, polycythemia, clubbing of the digits, and murmurs over the lung fields in the absence of cardiac disease. While rare, this diagnosis should come to mind in a patient presenting with cyanosis but a structurally normal heart on examination and on echocardiography.

Diagnosis

They may not be visible on a CXR or in 50% they can potentially be spotted on a CXR as well defined rounded or lobulated opacities. When a patient has cyanosis but no known lung or heart or liver disease, one must rule out PAVM via a contrast echocardiogram. A contrast echo is done by a cardiologist wherein agitated saline is injected through a vein while an echo is being performed. Normally, the microbubbles in the saline are absorbed by the capillary system in the lung so after being seen in the right heart only very few are seen in the left heart. However, in PAVM's they pass straight through to the pulmonary veins and left atrium. Therefore on echo, on injecting agitated saline into the arm veins, contrast bubbles noted to enter into the left atrium within 2–3 cardiac cycles raise the suspicion of pulmonary AVF.

Once this diagnosis is suspected, the next step is to do a cardiac catheterization or ideally, a multislice CT or an MRI angiogram to assess the nature, quantity and size of these pulmonary AV fistulae.

Treatment

Untreated, patients can develop worsening cyanosis and polycythemia and they remain at risk for right to left emboli and bleeding into the lung. Shunting of micro emboli bypasses the filtration function of the lungs and may result in development of transient ischemic attacks, a cerebrovascular accident, or a brain abscess. Most deaths attributable to PAVM are caused by stroke, cerebral abscess, hemoptysis, or hemothorax. Therefore treatment is needed. The problem is that treatment can be fairly problematic and needs to be individualized depending on the type and size.

In a simple pulmonary AVM with one large feeding vessel, the feeding artery can be closed in the catheterization laboratory by introducing some variety of vascular plug to occlude it (several types available—coils, plugs, detachable balloons, etc.). In complex malformations, surgical excision has resulted in cure of the disease with disappearance of cyanosis and clubbing when the lesion or lesions are localized to one or two segments of a lung. Diffuse lesions throughout the lungs are difficult to treat with endovascular techniques and are sometimes referred for lung transplant.

CORRECTED TRANSPOSITION OF THE GREAT ARTERIES (c-TGA/L-TGA)

Corrected transposition of the great arteries is one of those controversial cardiac anomalies—its name is not quite accurate and its management remains confusing. Essentially the ventricles are inverted. So although right atrial blood reaches the pulmonary artery, it does so via the left ventricle and pulmonary venous blood reaches the aorta via the RV. In isolated c-TGA therefore, patients are pink and essentially asymptomatic until the RV, which is not used to supporting the aorta, starts to fail.

Presentation

Most patients (90%) with c-TGA have associated anomalies such as a ventricular septal defect (VSD) (80%), pulmonary stenosis (PS) (40%), Ebstein anomaly of the tricuspid valve (10%) or complete heart block (2% chance of developing this per year). In addition to TR and/or right heart dysfunction, it is these associated lesions that can give rise to early symptoms, e.g., heart failure (VSD), exertional dyspnea (PS), cyanosis (VSD, PS), fatigue (heart block), etc.

Diagnosis

The clinical clue to the presence of c-TGA can be found on ECG which demonstrates q waves in lead V1 and absence of q waves in the left precordial leads (**Fig. 3**) and on CXR where the aorta can be noted to be prominent on the left side (L-posed aorta). Echocardiography is diagnostic and morphologically defines the ventricles, the presence or absence of VSD, PS, TR and RV dysfunction. Cardiac catheterization may be needed in selected cases to define the pulmonary artery or other anatomy before surgical intervention.

Treatment

Management is highly individualized depending on the permutation and combination of various symptoms and associated lesions. For instance, at one end of the spectrum, isolated c-TGA with normal functioning RV just needs annual follow-up with an ECG and echo while at the other end, patients with c-TGA VSD PS with cyanosis will need to undergo a complex double switch operation (atrial switch with Rastelli). Similarly patients with c-TGA and a VSD can either undergo a classical repair with VSD closure which leaves the RV as the systemic ventricle or a double switch operation along with the VSD closure which converts the RV into the pulmonary ventricle. Once the RV is made a low pressure chamber again, outcome is theoretically better as RV failure is unlikely to occur. However, the double switch operation is itself high-risk with significant mortality. So, risks versus benefits need to be weighed in each individual case and discussed as a group and with the family before a decision is taken.

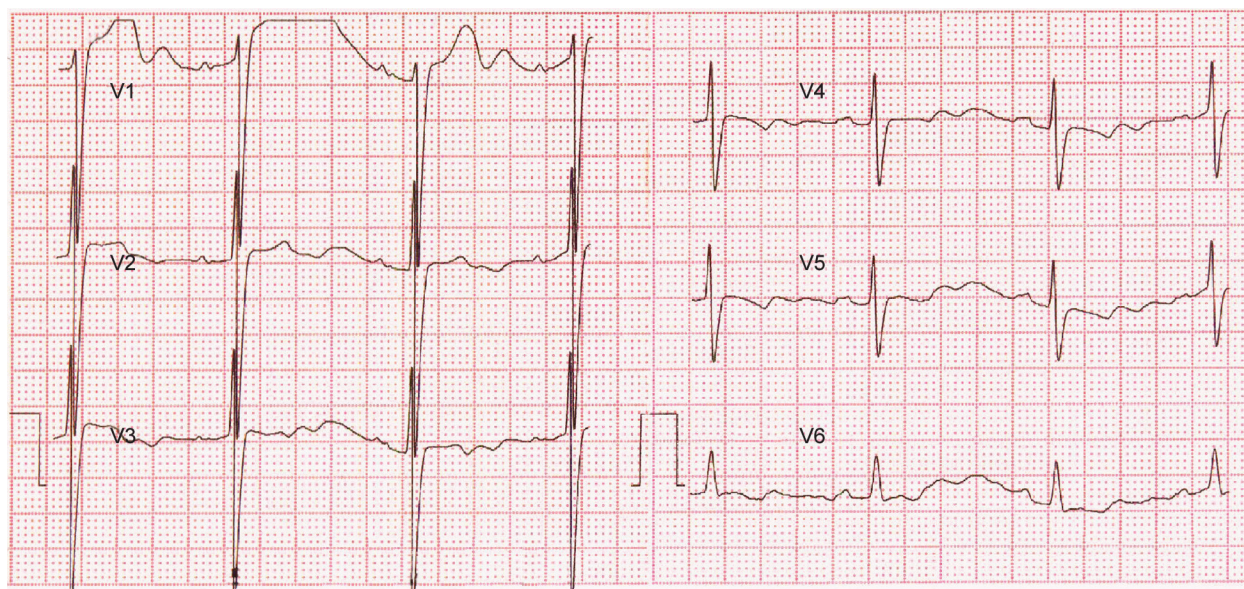


Figure 3 ECG in c-TGA demonstrating lack of q waves in leads V5 and V6

IN A NUTSHELL

1. *Ebstein anomaly*: Consider this diagnosis in a neonate with cyanosis, heart failure and massive cardiomegaly on CXR. Echocardiography is diagnostic. Treatment varies from nonintervention in asymptomatic older patients to varied surgeries in sick or cyanotic ones.
2. *Pulmonary AV fistulae*: Consider this diagnosis in a patient presenting with cyanosis but a structurally normal heart on examination and on echocardiography. Contrast echocardiography via a venous line will demonstrate microbubbles entering the left atrium rapidly.
3. *Corrected transposition of the great arteries*: This lesion is commonly detected due to its associations such as heart block, VSD's or pulmonary stenosis. Isolated, it generally needs no treatment. Its associated lesions dictate a complex treatment plan.

MORE ON THIS TOPIC

Hugh DA, David JD, Robert ES, Timothy FF. Moss and Adams Heart Disease in Infants, Children and Adolescents. 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2008.

Chapter 40.26

Admixture Lesions

Neeraj Awasthy, S Radhakrishnan

Congenital cyanotic heart disease (CCHD) with admixture physiology are defects in which deoxygenated systemic venous (SV) blood returning from the tissues mixes with the fully oxygenated pulmonary venous blood from the lungs in a common receiving chamber. These patients classically present as cyanosis with increased pulmonary blood flow.

CLASSIFICATION

Fully oxygenated pulmonary venous blood mixes with the deoxygenated SV blood resulting in a saturation somewhere in between that of pulmonary venous and SV blood oxygen saturation due to abnormal connections. When mixing is complete, the resultant oxygen saturation will depend on the relative contribution of the amount, of blood from each circulation. We would like to classify the admixture lesions into two further subsets: (1) Admixture lesion with complete mixing, (2) Admixture lesion with incomplete mixing.

Admixture Lesions with Complete Mixing

The effective saturation of admixed blood will be directly related to the amount of oxygenated blood from the lung (pulmonary blood flow) in the presence of normal cardiac output. Thus, the systemic arterial saturation will reflect the amount of pulmonary blood flow. In true sense this subset represents the *admixture physiology*.

Admixture Lesions with Incomplete Mixing

Incomplete mixing can arise on account of: (A) Restrictive communications between the deoxygenated and the oxygenated blood, e.g., transposition of great vessels (TGA) with intact septum, and restrictive interatrial communication, (B) Selective streaming of the deoxygenated and oxygenated blood as in double outlet right

ventricle (DORV) with subpulmonary ventricular septal defect (VSD) and no pulmonary stenosis, univentricular physiology without pulmonary stenosis. In true sense, this subset represents the *transposition physiology*.

Level of Mixing

Mixing at Pretricuspid Level

Venous level Total anomalous pulmonary or SV connection/drainage—supracardiac or intracardiac.

Atrial level Cardiac or coronary sinus type total anomalous pulmonary venous connection (TAPVC); single ventricle with atresia of one of the atrioventricular valves (tricuspid atresia, mitral atresia) without pulmonary stenosis.

Mixing at Post-tricuspid Level

Ventricular level DORV without pulmonary stenosis double outlet LV without pulmonary stenosis, single ventricle physiology (double inlet ventricle) without pulmonary stenosis.

Arterial level Persistent truncus arteriosus.

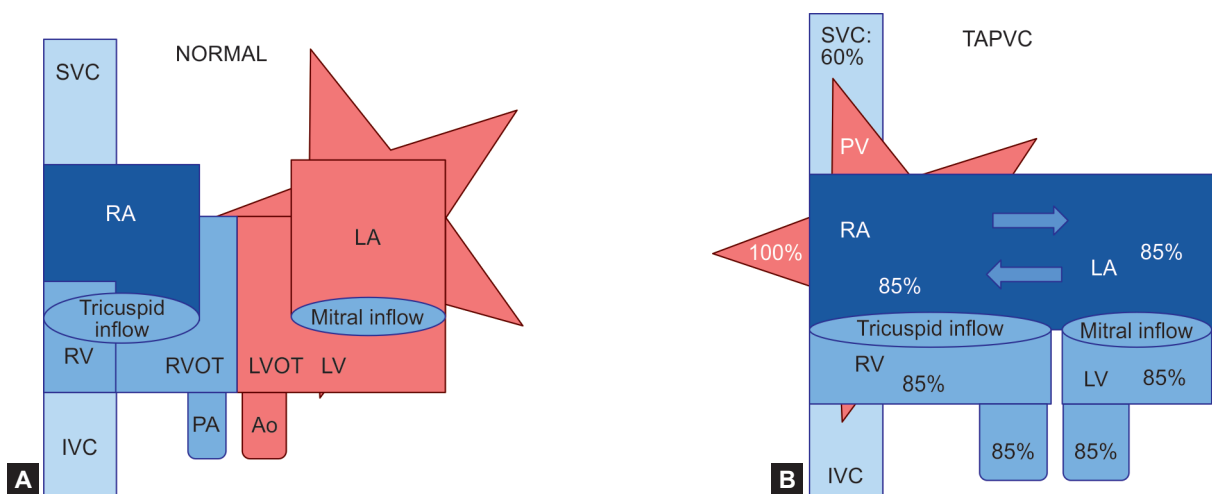
PHYSIOLOGY OF ADMIXTURE LESIONS

Complete Mixing

Arteriovenous oxygen difference will be about 25% in the basal state, for a normal cardiac index. In admixture lesions, the aortic saturation and the pulmonary artery (PA) saturation will be identical. If the aortic saturation is 85%, PA saturation can be assumed as 85% and pulmonary vein (PV) saturation as 100%. If we assume normal cardiac index, then the arteriovenous oxygen difference will be approximately 25%, that is, the SV saturation will be around 60%. $QP/QS = (AO \text{ saturation} - SV \text{ saturation}) / (PV \text{ saturation} - PA \text{ saturation}) = (85 - 60) / (100 - 85) = 25/15 = 1.67:1$ (Figs 1A and B).

Inherent Errors in Calculations

Let us assume a case of TAPVC If the superior vena cava (SVC) saturation in the above example is 70%, indicating a lesser arteriovenous oxygen difference and also reflecting a higher systemic



Figures 1A and B Schematic diagrams showing the hemodynamics. (A) Showing the schematic diagram of normal heart. (B) Schematic diagram in a case of TAPVC showing the drainage of PVs to right sided atrium with large interatrial communication. If we assume normal cardiac index, then the arteriovenous oxygen difference will be approximately 25%, that is, the SV saturation will be around 60%. $QP/QS = (AO \text{ saturation} - \text{systemic venous saturation}) / (PV \text{ saturation} - PA \text{ saturation}) = (85 - 60) / (100 - 85) = 25/15 = 1.67:1$

Abbreviations: RA, right atrium; LA, left atrium; RV, right ventricle; LV, left ventricle; IVC, inferior vena cava; SVC, superior vena cava; Ao, aorta; PA, pulmonary artery; RVOT, right ventricular outflow tract; LVOT, left ventricular outflow tract.

flow. The $Q_p/Q_s = (85-70)/100-85 = 15/15 = 1$. The aortic saturation in this case will still be 85%. The above mathematical example shows that the Q_p gets reduced by increased systemic saturations, thus there is more systemic flow than across the pulmonary vascular bed. But what is practical is that pulmonary venous blood gets directed to a common chamber, drains to right atrium, right ventricle (RV), PA and low resistance pulmonary vascular bed and thus chest X-ray shows pulmonary plethora. In no way is the pulmonary blood flow compromised and it is in fact higher than the basal state.

Let us look at the mathematical calculation example keenly The oxygen is used as an indicator for all the above calculations. The uptake of the oxygen across the bed (be it pulmonary or systemic vascular bed) decides the oxygen saturation across the bed (and this is assumed to be constant).

Let us discuss about Q_p The saturation in PA reflects a saturation of the mixing chamber (atrium) and the pulmonary venous saturation can never exceed 100, so although Q_p will increase because of dissolved oxygen, the ratio would never increase. Rather high Q_s because of high SV saturation will show falsely lower ratios.

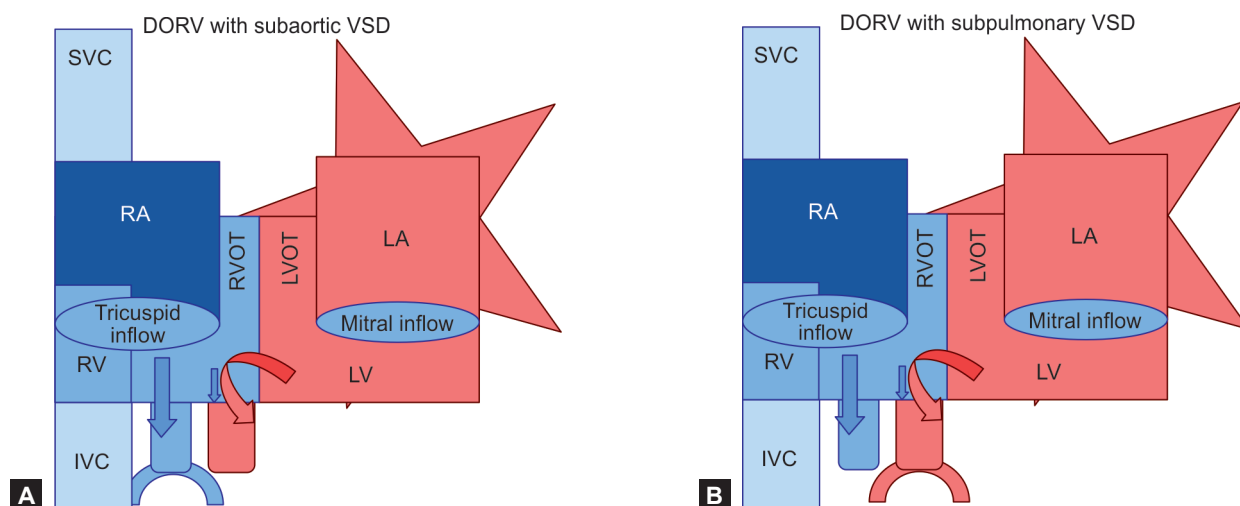
Thus there is an inherent error in calculations of Q_p/Q_s ratios (in the absence of looking at dissolved oxygen, which the ratios do not look at) for the admixture lesions. But still the calculations do guide to important observations.

Incomplete Mixing

In classical admixture lesions there is complete mixing in a common chamber and when this is not the case, this can result in two scenarios.

Streaming Phenomenon (Fig. 2)

- When the pulmonary venous return preferentially streams into the aorta (AO) it results in higher oxygen saturation in the AO than the PA (favorable streaming) (**Fig. 2A**)
- When the pulmonary venous return streams into the PA, this results in higher oxygen saturation in PA than AO (unfavorable streaming) (**Fig. 2B**)



Figures 2A and B (A) Schematic diagram of the heart with in a case of admixture lesion (DORV with VSD: subaortic), with streaming of the LV blood to the aorta and the right ventricular blood to the pulmonary circuit (favorable streaming). (B) DORV with subpulmonary VSD, with streaming of the LV blood to the pulmonary artery and systemic blood to aorta (unfavorable streaming)

Abbreviations: DORV, double outlet right ventricle; RA, right atrium; LA, left atrium; RV, right ventricle; LV, left ventricle; IVC, inferior vena cava; SVC, superior vena cava; RVOT, right ventricular outflow tract; LVOT, left ventricular outflow tract; VSD, ventricular septal defect.

- With identical pulmonary blood flow, streaming can considerably effect the systemic arterial oxygen saturation based on streaming in the common mixing chamber
- Systemic oxygen saturation is thus influenced both by the total pulmonary blood flow and the type and degree of streaming in the mixing chamber.

Restrictive Communication of the Mixing Chamber (Fig. 3)

The restrictive communication allows for the streaming effect. This is particularly true in pretricuspid admixture lesions. In normal physiology the inferior vena cava (IVC) blood gets directed to the interatrial communication, while the SVC blood gets directed to tricuspid valve. In the presence of restrictive interatrial communication in supracardiac TAPVC will result in more desaturated blood streamed to pulmonary artery, while infradiaphragmatic TAPVC will result in saturated blood to the left side. Similarly the absence of mixing in TGA at interatrial level will lead to the unfavorable streaming.

TOTAL ANOMALOUS PULMONARY VENOUS CONNECTION/DRAINAGE (TAPVC/TAPVD)

Total anomalous pulmonary venous connection (TAPVC) represents abnormal drainage of the pulmonary blood flow to the systemic circuit. Here in PVs forms a pulmonary venous confluence (PVC) and drain to the systemic vein. TAPVC can be divided into:

- *Supracardiac type:* Pulmonary venous confluence to innominate vein or azygous vein
- *Cardiac type:* PVC to the coronary sinus
- *Infracardiac type:* PVC to the IVC. More than one type may coexist in a patient.

Physiology

Right atrium is the mixing chamber irrespective of the site of drainage of TAPVC. The right atrium, RV, pulmonary artery, left atrium, left ventricle (LV), and aortic oxygen saturations are identical. Systemic saturation indirectly reflects the blood flow

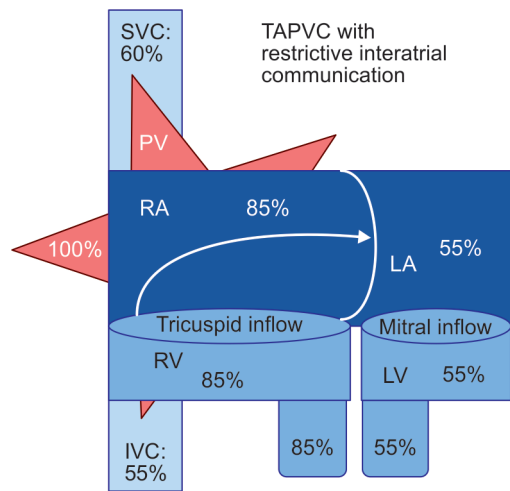


Figure 3 Schematic diagram of the heart with restrictive interatrial communication in a case of admixture lesion (TAPVC), with bulging of the interatrial septum to the left. IVC blood gets directed to the restricted PFO, the only cardiac output and hence the systemic flow is restricted

Abbreviations: RA, right atrium; LA, left atrium; RV, right ventricle; LV, left ventricle; IVC, inferior vena cava; SVC, superior vena cava.

across pulmonary vascular bed hence low systemic saturation suggests decreased pulmonary blood flow because of pulmonary vascular disease, while good aortic saturations indicate good pulmonary blood flow.

Streaming in Total Anomalous Pulmonary Venous Connection

Superior vena cava and coronary sinus blood is directed to the tricuspid valve (TV) and IVC blood to the atrial septum hence to the left atrium. Hence supracardiac TAPVC draining into SVC or to coronary sinus streams selectively to the TV, RV, and into PA (unfavorable streaming) and infradiaphragmatic TAPVC draining to IVC selectively streams across the atrial septal defect (ASD) (favorable streaming). Streaming phenomenon results in dissimilar saturation in AO and PA. Causes of low arterial oxygen saturation in TAPVC include: reduced pulmonary blood flow due to pulmonary vascular disease; pulmonary venous desaturation due to pulmonary venous hypertension (PVH) because of obstruction to the channel, site of drainage with or without individual PV obstruction; PVH and unfavorable streaming.

Patients with infradiaphragmatic obstructed TAPVC can maintain fair systemic saturation despite being moribund due to PVH and pulmonary edema due to obstruction in pathway of pulmonary venous blood commonly associated with intra-diaphragmatic TAPVC (unfavorable anatomy) because of favorable streaming.

Associated Lesions and Interventions

Associated pulmonary venous stenosis may decrease the flow across the pulmonary vascular bed; hence coexisting pulmonary venous stenosis may get masked. Alternatively opening of the ductus by prostaglandin may lead to pulmonary edema in this setting.

Clinical Features

Clinical presentation and the age of presentation of TAPVC depends upon the presence and absence of obstruction. *Obstructive TAPVC* presents early with respiratory distress, severe pulmonary venous and arterial hypertension and need to be operated urgently. In an infant of *TAPVC without obstruction* where there is classical

example of admixture physiology on account of good mixing generally occurs at the atrial level, the cyanosis may be subtle. One has to keenly observe for the presence of same. Clinical features resemble that of ASD with left to right shunt. There is wide and fixed splitting of the second heart sound. As there is increased flow across the tricuspid valve a mid diastolic murmur across the tricuspid valve is heard. Because of increased pulmonary blood flow ejection systolic murmur across the pulmonary valve is heard. If any patient with the findings of ASD has cyanosis, the first bedside diagnosis should be TAPVC. Also one may hear the flow through the confluence, e.g., venous hum in the neck or second right intercostal space in case of supracardiac TAPVC.

Investigations

Electrocardiography

Right ventricular hypertrophy (RVH) of the volume overload type (i.e., rsR' in V1) and occasional right atrial hypertrophy (RAH) are present.

Chest X-ray

Cardiomegaly with dilated RA and RV is present with increased pulmonary vascular markings (**Figs 4 and 5**). In supracardiac type the dilated vertical vein, innominate vein and SVC may give classical *Snowman* sign or figure-of-8 configuration. This is rarely seen before 4 months of age. In obstructed TAPVC, the heart size is normal or slightly enlarged. There are features of pulmonary edema (i.e., diffuse reticular pattern and Kerley's B lines). These findings may be mimic pneumonia or hyaline membrane disease of the newborn.

Echocardiography

Echocardiography (**Fig. 6**) is generally diagnostic in most of the patients rarely, CT angiogram may be required to delineate the individual veins.

Management

Medical Management

Intensive anticongestive measures with digitalis and diuretics should be provided for infants without pulmonary venous obstruction. Metabolic acidosis should be corrected, if present.



Figure 4 Chest X-ray frontal view showing characteristic *Snowman* appearance or *Figure of 8* in patient with supracardiac TAPVC draining into left innominate vein through vertical vein. Left upper heart border is formed by ascending vertical vein, superior border by dilated innominate vein and right upper border by dilated SVC

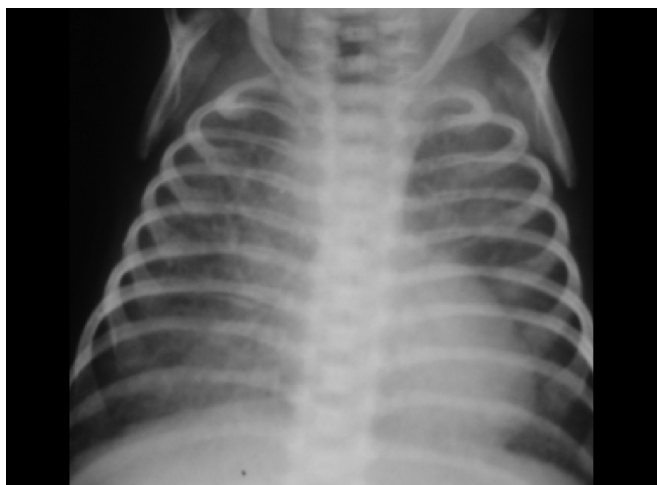


Figure 5 Chest X-ray in obstructed TAPVC in an infant. There is diffuse bilateral pulmonary venous congestion because of pulmonary venous obstruction

Infants with severe pulmonary edema (resulting from the infracardiac type and from other types with obstruction) should be intubated and receive ventilator support with oxygen and positive end-expiratory pressure, if necessary, before cardiac catheterization and surgery. In some patients with pulmonary hypertension, prostaglandin E1 (PGE 1) can increase systemic flow by keeping the ductus open. In the infracardiac type, PGE 1 may be helpful in maintaining the ductus venosus open. If the size of the interatrial communication appears small and immediate surgery is not indicated, balloon atrial septostomy or blade atrial septostomy may be performed to enlarge the communication.

Surgery

Corrective surgery in the form of pulmonary venous rerouting is necessary for all patients with this condition. Obstructed TAPVC should be operated on soon after diagnosis. Nonobstructed TAPVC is usually operated on between 4 and 6 months.

TOTAL ANOMALOUS SYSTEMIC VENOUS DRAINAGE

Clinical features of TASVD will resemble essentially that of TAPVC. There is a strong association of the anomaly with left isomerism with associated features: such as symmetrical *midline* liver (on palpation or X-ray films), discordant cardiac apex and stomach bubble (on chest X-ray films), biliary atresia in a neonate with congenital heart defects, and symmetrical main stem bronchi on chest X-rays. Almost 70% of the hearts have ectopic atrial rhythm with a superiorly oriented P axis (-30° to -90°). With the presence of endocardial cushion defect, a superior QRS axis may be present.

DOUBLE OUTLET VENTRICLE

Double outlet right (Fig. 7) or left ventricle (DORV/DOLV) with subpulmonary VSD and no pulmonary stenosis presents with congestive heart failure (CHF) and cyanosis in infancy. As such these lesions can be kept in differential diagnosis of patients with cyanosis and increased pulmonary blood flow. DORV can have subaortic VSD or subpulmonic VSD. In this admixture lesion mixing chamber is RV but often complete mixing does not occur and thus RV acts as a conduit with LV pumping through it to the great vessels and little opportunity to effect complete mixing in RV. As the flow in RV is essentially in systole with both ventricles contacting, thus incomplete mixing secondary to streaming is commonly seen in DORV with following implications:

- In DORV with subaortic VSD there is favorable streaming with saturated LV blood enters the AO and RV blood enters the PA, this results in saturation significantly higher than PA. Thus DORV with subaortic VSD presents like a large left to right shunt VSD, as the desaturation is mild and cyanosis may not be clinically apparent (Fig. 2A).
- In VSD with subpulmonic location there is unfavorable streaming with PA saturation more than the AO. This subgroup presents clinically as transposition of great arteries with VSD, with significant systemic desaturation (cyanosis) despite increased pulmonary blood flow (Fig. 2B).
- Thus, in DORV the systemic saturation may not accurately reflect the pulmonary blood flow and systemic desaturation is decided by streaming and associated anomalies.

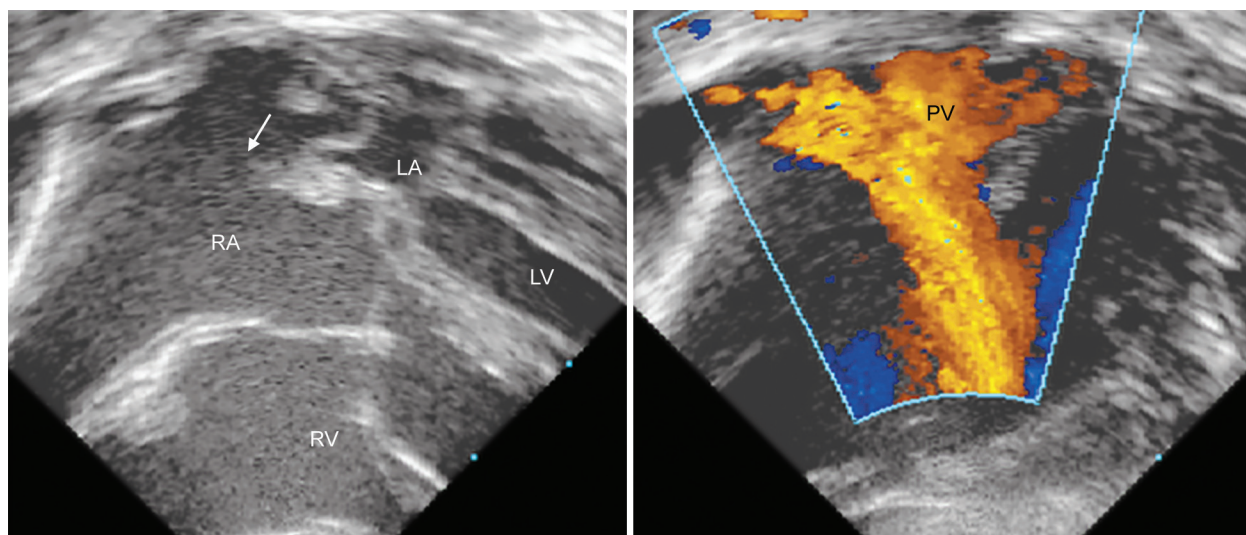


Figure 6 Echocardiogram with color compare in subcostal coronal view showing the drainage of the pulmonary venous blood to the right atrium with dilated right atrium and right ventricle because of malaligned interatrial septum
Abbreviations: RA, right atrium; LA, left atrium; RV, right ventricle; LV, left ventricle; PV, pulmonary valve.

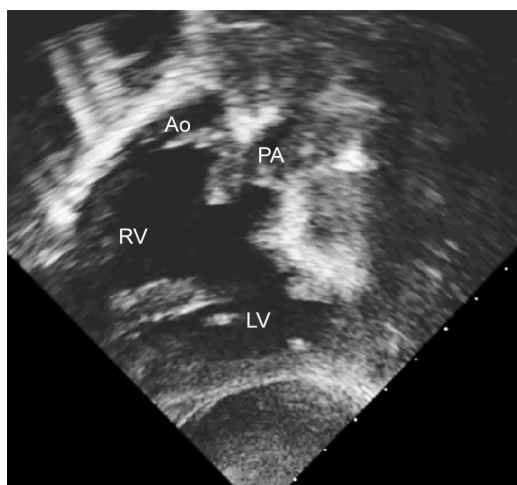


Figure 7 2D echocardiogram in apical 4-chamber view with anterior tilt showing both the great arteries: aorta and pulmonary artery arising from right ventricle in a child with DORV
Abbreviations: PA, pulmonary artery; Ao, aorta; LV, left ventricle; RV, right ventricle; DORV, double outlet right ventricle.

Clinical Features

Clinical features in a case of DORV reflect the location of the VSD in relation to the great arteries; and the relationship of the great arteries. The presence of cyanosis in these lesions is adjudged by two physiological parameters discussed above: the streaming and the amount of pulmonary blood flow.

Subaortic Ventricular Septal Defect without Pulmonary Stenosis

Pulmonary blood flow (PBF) is increased and CHF may result. Therefore, clinical pictures resembles those of a large VSD with pulmonary hypertension and CHF. The child may have growth retardation, tachypnea, hyperactive precordium, a loud S_2 , and a VSD-type (holosystolic or early systolic) murmur. An S_3 and apical diastolic rumble may be audible. ECG may reveal superior QRS axis (i.e., -30° to -170°). RVH or biventricular hypertrophy (BVH), as well as left atrial hypertrophy (LAH), is common. Occasionally, first degree AV block is present. Chest X-ray images show cardiomegaly with increased pulmonary PA segment.

Subpulmonary Ventricular Septal Defect (Taussig-Bing Syndrome)

Clinical pictures in this setting resembles those of TGA. Combination of cyanosis with CHF (TGA physiology), may be because of the selective streaming of the VSD to the pulmonary vascular bed and the SV flow to the systemic arterial circulation. This group present the earliest. Growth retardation and severe cyanosis with or without clubbing are common findings. The S_2 is loud, and a grade 2–3/6 systolic murmur is audible at the upper left sternal border. An ejection click and an occasional PR murmur (as a result of pulmonary hypertension) may be audible. The ECG shows right axis deviation (RAD), RAH, and RVH. Chest X-ray shows cardiomegaly with increased pulmonary vascular markings and a prominent PA segment.

Doubly Committed or Noncommitted Ventricular Septal Defect

Cyanosis of a mild degree is present and the PBF increases.

In general, in a case of CHF with cyanosis presence of extreme RAD on electrocardiogram and presence of narrow pedicle on chest X-ray (pointing to malposed vessels) may be present in some cases and when present are important clinical clue to the diagnosis of DORV with malposed vessels.

Management

The plan of management is essentially surgical and is decided by considering the location of the VSD in relation to great arteries.

SINGLE VENTRICLE

Admixture physiology in single ventricle (**Fig. 8**) may be discussed as below.

Pretricuspid Admixture Lesions

These patients include mitral atresia and tricuspid atresia without pulmonary stenosis. In these setting atria forms the mixing chamber with fairly good mixing as seen in admixture physiology. The manifestations depend upon the degree of pulmonary blood flow.

Post-tricuspid Admixture Lesions

- In single-ventricle physiology both favorable and unfavorable streaming is often seen and does not necessarily depend on the ventricular morphology or the great vessel relation.
- Patients with double inlet left ventricle (DILV) with aorta arising from the left-sided and anterior rudimentary RV outflow chamber (inverted) have SV blood preferentially directed into the PA and pulmonary venous blood to the aorta (preferential streaming).
- Patients with aorta from a right-sided and anterior rudimentary RV outflow chamber (noninverted) may have *unfavorable* streaming.
- These single ventricles have a mixing chamber as the ventricles.
- In this setting the arterial oxygen saturation will reflect pulmonary blood flow.

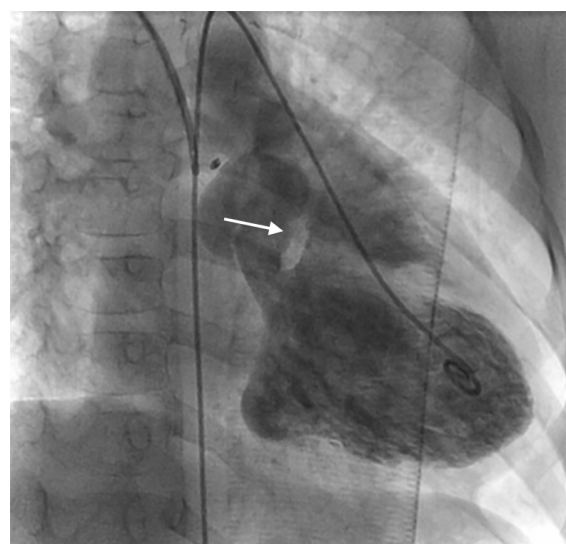


Figure 8 LV angiogram in LAO cranial view in a case of single ventricle with atretic left component showing the atretic left component marked by arrow

Clinical Manifestations

Cyanosis may be present from birth, depending upon the pulmonary blood flow.

With *increased PBF*, physical findings resemble those of VSD or may be transposition of great vessels: mild cyanosis and CHF with growth retardation; single or narrowly split S_2 with a loud P_2 . A grade 3–4/6 long systolic murmur is audible along the left sternal border. An S_3 or apical diastolic rumble may be present. In case of pulmonary hypertension diastolic murmur of PR may be present along the upper left sternal border.

Physical findings in *single ventricle with decreased PBF* resemble tetralogy of Fallot (TOF). Moderate to severe cyanosis is present. CHF is not present. Clubbing may be seen in older infants and children. The S_2 is loud and single. A grade 2–4/6 ejection systolic murmur may be heard at the upper right or left sternal border.

ECG

An unusual ventricular hypertrophy pattern with similar QRS complexes (monomorphic) across most or all precordial leads is common (e.g., RS, rS, QR pattern). Abnormalities in septal depolarization represented by abnormal Q waves: Q waves in the right precordial leads, no Q waves in any precordial leads, or Q waves in both the right and left precordial leads. Either first- or second-degree AV block may be present. Arrhythmias are not infrequent (e.g., SVT, wandering pacemaker).

TRUNCUS ARTERIOSUS

Persistent truncus arteriosus (PTA) is defined as common arterial trunk arising from base of heart, gives origin to aorta, pulmonary arteries, and coronaries (**Fig. 9**). VSD with truncus is usually large.

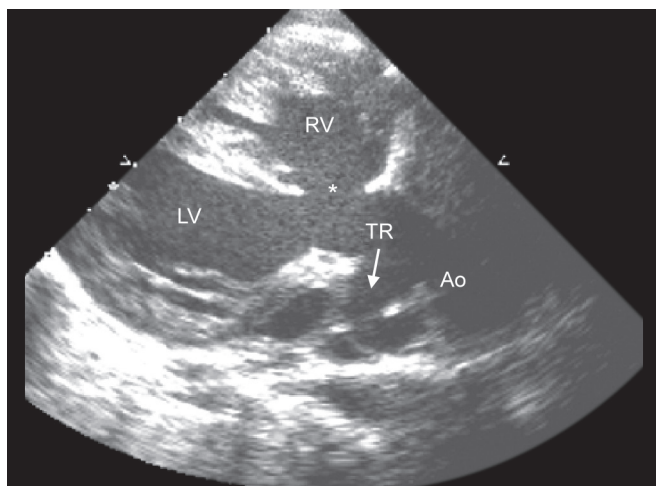


Figure 9 Parasternal long axis views with anterior tilt in a case of truncus arteriosus showing large outlet ventricular septal defect (*), over-riding common trunk. The main pulmonary artery arises posteriorly (arrow)
Abbreviations: Ao, aorta; TR, truncus; LV, left ventricle; RV, right ventricle.

It results from absent or deficient outlet septum, perimembranous part of septum is usually intact with truncus arteriosus, in 25% of cases defect may extend to membranous area. Rarely the VSD may be restrictive or even absent. This condition is described in detail in Section 40.24.

IN A NUTSHELL

1. Admixture physiology are defects in which deoxygenated SV blood mixes with the fully oxygenated pulmonary venous blood from the lungs in a common receiving chamber. These patients classically present as cyanosis with increased pulmonary blood flow.
2. The mixing can be complete or incomplete; and can occur either at pretricuspid or post-tricuspid levels. Clinical features will vary accordingly.
3. TAPVC is the most common admixture lesion representing abnormal drainage of the pulmonary blood flow to the systemic circuit. Here in PVs forms a pulmonary venous confluence (PVC) and drain to the systemic vein. TAPVC can be divided into: *Supracardiac type*: Pulmonary venous confluence to innominate vein or azygos vein; *Cardiac type*: PVC to the coronary sinus; and *infracardiac type*: PVC to the IVC. More than one type may coexist in a patient.
4. Double outlet ventricle, single ventricle, and truncus arteriosus are the other common admixture lesions described in this chapter.
5. Admixture lesions are fairly important subgroup and their hemodynamic gets governed by pulmonary blood flow in classical lesions and also gets influenced by streaming, degree of obstruction to mixing and associated lesions.
6. Operability needs to be individualized to each respective admixture lesion. In general CHF, cardiomegaly and arterial saturation 85% or more favor operability.

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Chapter 40.27

Hypoplastic Left Heart Syndrome

Joseph John Vettukattil

Hypoplastic left heart syndrome (HLHS) refers to a spectrum of heart defects where hypoplasia (underdevelopment) of the left heart structures, e.g., left atria, left ventricle, ascending aorta or the aortic arch occur secondary to either stenosed, atretic or hypoplastic morphological left sided valves, resulting invariably in early neonatal death, unless *single ventricle* palliative procedure is undertaken to recruit the right ventricle to function as the systemic ventricle. Exceptionally the entire left heart may be hypoplastic without evidence of any structural obstruction. An obligatory atrial communication, or persistence of a decompressing vein that shunts pulmonary venous flow to the right side is mandatory for survival.

Hypoplastic left heart syndrome occurs in 0.16–0.36 per 1000 livebirths or 7–9% of all congenital heart defects. It is more common in boys.

ETIOPATHOGENESIS

Though its cause is multifactorial, familial cases with autosomal recessive, dominant and also X-linked modes of inheritance with variable penetrance and phenotypes have been reported. Increased occurrence has been noted in: Deletion of distal 11q (Jacobsen syndrome) and trisomies 13 and 18, besides Turner syndrome. Genetic mutations impairing prograde flow in developing left ventricle have been identified in 4 genes: *GJAI* (Connexin43, 6q22), cardiac transcription factor *NKX2-5* (5q35), *NOTCH1* (9q34) and *HAND1* (5q33). Moreover, definitive evidence has identified 8 genetic loci like 14q23 where a mutation results in HLHS and bicuspid aortic valve in the same family. The timing of the causative insult occurs during aortic and mitral valve development by limiting the blood flow through the left heart, which is vital for its development. Retrograde perfusion in the ascending aorta via patent ductus arteriosus (PDA) maintains the blood flow to the brain and coronary arteries (*duct dependent*).

Premature closure or absence of the patent foramen ovale (PFO) is a theoretical cause of HLHS as it prevents the inferior vena caval blood entering the left atrium; the fetal pulmonary blood flow alone is insufficient to promote development of the left heart structures.

Anatomic Considerations

Considerable variations in the size and nature of the aortic and mitral valves (atretic, hypoplastic or severely stenotic) are noted. It is important to exclude a supramitral membrane which when detected may change the management of the child. The mitral subchordal apparatus may be fused or have secondary chordae obstructing the outflow tract. In extreme cases, the whole left heart structures may be miniaturized with no functional components. The left ventricle is severely hypertrophied with a slit-like cavity, especially when the mitral valve is atretic. Endocardial fibroelastosis is often present depending on the degree of inflow and outflow tract obstruction. There is varying degree of subaortic or aortic valve obstruction with a narrow ascending aorta. Atrial or pulmonary venous anomalies including pulmonary vein obstruction or TAPVD may be associated.

PATHOPHYSIOLOGY

Fetal Circulation

In HLHS, the oxygenated placental blood from inferior vena cava (IVC) does not cross the fossa ovalis into the left atrium; instead, it mixes with the superior vena caval blood in the right atrium (RA). Obstruction in left heart, either at the mitral or aortic valve level, causes the pulmonary venous return to preferentially flow from the left atrium (LA) into the RA. The vena caval and pulmonary venous blood along with the coronary sinus flow enters the right ventricle and the pulmonary artery. A wide PDA and high pulmonary vascular resistance (PVR) drives most of the blood into the aortic arch. This flow is then distributed to the head and neck vessels, coronary arteries and the descending aorta. The distribution of blood into each vascular bed is determined by the relative resistance in each system. Thus the fetal circulation in HLHS differs from the normal fetus in the following manner:

- Larger PDA with higher PO₂
- Cerebral blood flow with relatively lower PO₂
- Higher PO₂ in the pulmonary arterial blood
- Retrograde coronary blood flow containing low PO₂ via a long curved channel from aortic arch supplying blood to the brain and upper body before supplying the coronaries.

Postnatal Circulation

The uniqueness of fetal circulation continues in the newborn with HLHS. The main changes at birth are the expansion of the lungs and increasing pulmonary blood flow delivered at systemic pressures. This leads to higher pulmonary venous return and increase in obligatory left to right shunt across the atrial septum. The right heart receives normal systemic venous return in addition to the increased pulmonary venous return. This causes the normally compliant right heart to dilate. Initially the RV systolic function is well maintained; but when stretched beyond the Starling curve, right heart dysfunction occurs with tricuspid valve regurgitation (TR).

Flow being inversely proportional to resistance (Ohm's law), the postnatal reduction in PVR occurring due to expansion of lung fields and regression of the pulmonary arterial wall thickness, leads to increased pulmonary blood flow. As the pulmonary blood flow increases, systemic blood flow, including coronary perfusion decreases, causing metabolic acidosis, decreased organ perfusion with oliguria and coronary ischemia. Unless the pulmonary blood flow is carefully controlled, the situation rapidly deteriorates, ending in cardiac arrest.

In HLHS, the sizes of the interatrial communication and ductus arteriosus determine the relative flow in systemic and pulmonary circulation, which in turn affects the systemic organ perfusion, coronary perfusion and pulmonary blood flow. The additional presence of varying degrees of arch hypoplasia and coarctation further compromises cerebral and retrograde coronary blood flow.

CLINICAL FEATURES

Neonatal Presentation

Most newborns with HLHS appear well at birth. The oxygen saturation is typically in the low 90s. As the PVR falls, tachypnea and tachycardia set in. Tachypnea with CO₂ washout further augments pulmonary blood flow and alveolar O₂ bringing the saturation to high 90s, a sign of impending cardiac decompensation. Vasoconstriction developing in neonates increases systemic vascular resistance (SVR) which in turn increases pulmonary blood flow. Feeble pulses and decreasing body perfusion with tachypnea, hypothermia, oliguria, or large liver are adequate reasons for Doppler ultrasound examination in neonates even before the development of lactic acidosis, pulmonary edema,

worsening saturation, ending in cardiac arrest. Murmur is rarely present due to TR. Very rarely a HLHS patient with restricted atrial communication and PDA may present at few weeks of age with severe pulmonary hypertension and desaturation.

Postnatal Diagnosis

Hypoplastic left heart syndrome must be suspected in any neonate, not diagnosed by fetal ultrasound presenting with tachypnea, tachycardia, feeble pulses and hypothermia. All such neonates should receive prostaglandin E1 infusion to maintain ductal patency while awaiting echocardiogram and parental decision for further referral and management. Other investigations may be supportive.

INVESTIGATIONS

Chest Radiograph

Cardiomegaly with increased pulmonary vascular markings; findings of pulmonary edema in the presence of restricted PFO or obstructed pulmonary veins. A large heart often suggests associated TR and right heart dilatation.

ECG

Sinus tachycardia with right-axis deviation, right atrial enlargement, and right ventricular hypertrophy with a qR configuration in the right precordial leads. Reduced LV forces, with ST-T wave changes suggestive of myocardial ischemia may be seen.

Echocardiography and Doppler Ultrasound

These reveal the following *diagnostic* information: Hypoplastic left ventricle and ascending aorta, the size of the mitral and aortic annulus; the length, morphology and function of LV, the mechanism of LVOT obstruction, the size of the ascending aorta, the morphology and mechanism of TR if present; the anatomy and direction of flow of the atrial communication, and direction of the ductal flow, and the presence and site of arch obstruction.

TREATMENT

The management of HLHS can be highly challenging as it involves continuous and compassionate care, staged palliation through multiple surgical interventions, frequent hospitalization, medications, and treatment of complications associated with significant mortality. Parents should be mentally prepared and encouraged to take treatment decisions by providing them with adequate details about each of these approaches and outcomes.

Initial Supportive Therapy in Neonatal Period

First Objective

Ductal patency is to be maintained to provide adequate blood flow to the systemic circulation and coronary perfusion by administering prostaglandin E1 infusion (5 ng/kg/min) with appropriate care and monitoring to avoid a significant dilatation of pulmonary circulation.

Second Objective

Pulmonary blood flow must be regulated so as to avoid an early onset of increased pulmonary vascular resistance (PVR). Factors affecting PVR include lung maturity, age, metabolic status, arterial PCO₂ and PO₂ levels, pH, cardiac functional status, the presence of TR, end diastolic pressure of the ventricles and restriction across the atrial septum. PVR is extremely sensitive to alveolar oxygen concentration. Hence, oxygen administration should not be based on hypoxia but the presence of parenchymal lung disease or pulmonary edema. Oxygen is best avoided if the lungs are normal and the neonate should be managed in room air.

Permissive hypercapnea with higher PaCO₂, an important aspect of managing PVR, often requires elective total ventilatory support by day 3 or 4 with hypoventilation, or the addition of nitrogen or carbon dioxide to the inspiratory circuit. Prior to intubation, the administration of nitrogen via hood may be practiced. Supportive measures are outlined in **Table 1**.

Surgery

Norwood (Stage I) Procedure (Palliative)

The main objectives are to control excess pulmonary blood flow and improve and maintain unobstructed systemic blood flow. Usually it is performed on day 5 of life with the falling of PVR in stabilized neonates on ventilator support. It consists of the following surgical maneuvers:

- Atrial septectomy to provide unrestricted atrial mixing
- PDA closure
- Creation of main pulmonary artery—aortic connection with a restrictive PA-aorta shunt placement to provide adequate pulmonary blood flow.

These stage I operated children with HLHS are managed in the same palliative manner as other congenital heart conditions with single ventricle with creation of bidirectional superior cavopulmonary artery anastomosis and subsequent completion of Fontan with a total cavopulmonary connection.

Sano modification of the Norwood procedure Increasingly adopted by many centers for better survival outcome between the first stage and cavopulmonary anastomosis, Sano procedure entails the insertion of a Gore-Tex graft between the RV and PA to provide restricted pulsatile pulmonary blood flow instead of a conventional modified aortopulmonary shunt. Major concerns include: single systemic RV scarring and branch pulmonary arterial distortions.

Hybrid and Other Approaches

Bilateral banding of the pulmonary arterial branches with stent placement in the ductus arteriosus is performed to reduce the high mortality associated with stage I Norwood reconstruction. In preterm babies with HLHS, long-term ductal patency with prostaglandin infusion instead of ductal stenting is rarely resorted to.

Transplantation

The alternative to staged Norwood procedure is neonatal heart transplantation with nearly similar survival outcomes and long-term complications. Fetal—prenatal interventions to prevent fetal hypoplasia of LH by relieving aortic valve stenosis or creating atrial septal defects are under investigation.

Table 1 Supportive measures in a newborn with hypoplastic left heart syndrome

Parameters	Medications	Monitoring
Metabolic acidosis	Sodium bicarbonate infusion	Serial arterial blood gas and acid-base, electrolytes
Oxygen saturations in the low 80s	Oxygen	
Systemic vasodilatation and regulation of PVR without compromising blood flow to other vital organs	Judicious use of inotropes, keeping in mind the potential benefits of vasodilatation in regulating PVR	Arterial pressures; ECHO Doppler studies
Diuretics	Renal perfusion	Adequate urine output

OUTCOME

Prenatal

The risk of intrauterine death is less than 5% and nearly half of pregnancies get terminated. Of the remaining 50–55%, the majority (80%) are born by normal vaginal delivery.

Postnatal

Without palliative surgery, all die within the first few weeks. In advanced countries, depending on the practice at a given cardiac center about 90% are palliated with Norwood or Sano procedure while others undergo hybrid procedure or heart transplantation; only a small proportion (10–15%) die preoperatively waiting for interventional treatment.

The 5-year survival of children born with HLHS after 3 major operations before school age and with the first 2 operations in their first year has significantly improved to around 60–70% with significant morbidity. Survivors exhibit reduction in exercise tolerance, delayed growth and motor development, low-normal intelligence, high-risk of sudden death, need for repeat hospitalizations, chronic medications and complications of single ventricle physiology.

MORE ON THIS TOPIC

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IN A NUTSHELL

1. Hypoplastic left heart syndrome (HLHS) refers underdevelopment of the left heart structures, e.g., left atria, left ventricle, ascending aorta or the aortic arch.
2. Presence of an obligatory atrial communication or persistence of a decompressing vein that shunts pulmonary venous flow to the right side is mandatory for survival.
3. HLHS must be suspected in any neonate, presenting with tachypnea, tachycardia, feeble pulses and hypothermia.
4. All such neonates should receive prostaglandin E1 infusion to maintain ductal patency while awaiting echocardiogram and parental decision for further referral and management.
5. Early palliative surgery is recommended within first week of life.

Chapter 40.28

Pulmonary Arterial Hypertension

Nageswara Rao Koneti

Sir William Harvey was the first to describe importance of right ventricular (RV) function in 1616. However, for many years, the emphasis in the research was placed on the left ventricular (LV) physiology. The clinical importance of RV function in heart failure, congenital heart disease and pulmonary hypertension came into light only between 1950s and 1970s. The true incidence of idiopathic pulmonary arterial hypertension (IPAH) is unknown; however, 2.2 new cases per million per year are identified. Pulmonary arterial hypertension (PAH) may be idiopathic or secondary. PAH secondary to congenital and other structural or systemic disease is still the leading causes globally. The etiology of IPAH is unknown and poorly understood. The diagnosis is by exclusion after complete evaluation to rule out secondary causes. The natural history of IPAH appears to be still guarded even in this era. The National Institutes of Health Registry showed over all median survival of 2.8 years after the diagnosis, whereas in children median survival after diagnosis is reported to be only 10 months. However, the prognosis appears to be slightly better with the current understanding and available medications.

DEFINITION

Pulmonary hypertension (PAH) is defined as mean pulmonary arterial pressures more than 25 mm Hg at rest or more than 30 mm Hg during exercise. Neonates and infants below 3 months of age are excluded in the definition due to physiological interference of neonatal pulmonary vascular resistance.

Persistent pulmonary hypertension of newborn is a pulmonary parenchymal disease due to various mechanisms leading to maladaptation in the postnatal period or in utero due to unknown mechanism. This condition is characterized by increased pulmonary vascular resistance, severe hypoxemia and right to left shunt across foramen ovale and arterial ductus.

Hyperkinetic pulmonary hypertension is due to increased pulmonary blood flow, congenital heart disease, e.g., ventricular septal defect. Pulmonary venous hypertension is caused by either obstruction or dysfunction in the left side of the heart leading to increased pulmonary capillary wedge pressures (postcapillary pulmonary hypertension), e.g., mitral stenosis, LV dysfunction, etc. Pulmonary vascular disease due to congenital heart disease will be developed over the period of time due to left to right shunt referred as Eisenmenger syndrome.

Clinical classification of pulmonary hypertension is shown in **Box 1**. The clinical conditions with PAH are classified according to pathological, pathophysiological and therapeutic characteristics into five groups (4th World Symposium on PAH, 2008).

PATHOPHYSIOLOGY

Pulmonary arterial hypertension is a disease of pulmonary vascular tone. The important features are abnormal muscularization of distal pulmonary arteries at the alveolar duct and wall levels and reduction in their number. Progressive intimal hyperplasia is commonly seen in older children and adults leading to plexiform lesions and occlusive changes (**Figs 1A to C**). PAH is a vasculopathy involving small arteries and arterioles. The changes include

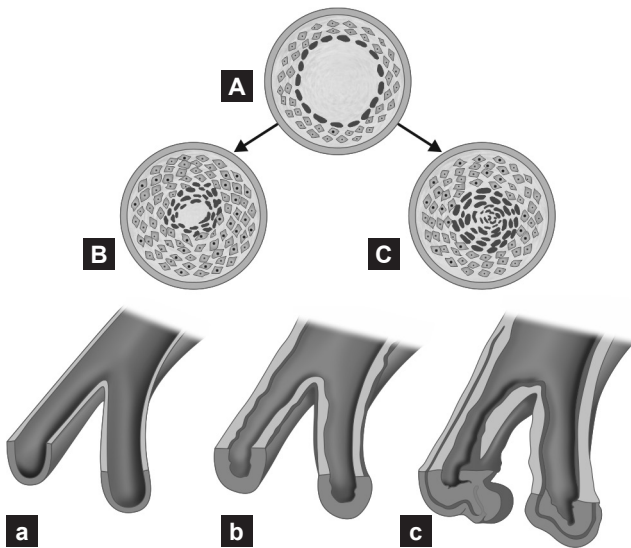
BOX 1 Causes and nice clinical classification of pulmonary hypertension (modified from past Dana Point classification)

- Pulmonary arterial hypertension
 - Idiopathic PAH
 - Heritable PAH
 - BMPR2
 - ALK-1, ENG, SMAD9, CAV1, KCNK3
 - Unknown
 - Drug and toxin induced
 - Associated with:
 - Connective tissue disease
 - HIV infection
 - Portal hypertension
 - Congenital heart diseases
 - Schistosomiasis
 - Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
 - Persistent pulmonary hypertension of the newborn (PPHN)
- Pulmonary hypertension due to left heart disease
 - Left ventricular systolic dysfunction
 - Left ventricular diastolic dysfunction
 - Valvular disease
 - Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
- Pulmonary hypertension due to lung diseases and/or hypoxia
 - Chronic obstructive pulmonary disease
 - Interstitial lung disease
 - Other pulmonary diseases with mixed restrictive and obstructive pattern
 - Sleep-disordered breathing
 - Alveolar hypoventilation disorders
 - Chronic exposure to high altitude
 - Developmental lung diseases
- Chronic thromboembolic pulmonary hypertension (CTEPH)
- Pulmonary hypertension with unclear multifactorial mechanisms
 - *Hematologic disorders*: Chronic hemolytic anemia, myeloproliferative disorders, splenectomy
 - *Systemic disorders*: Sarcoidosis, pulmonary histiocytosis, lymphangioma, leiomyomatosis
 - *Metabolic disorders*: Glycogen storage disease, Gaucher disease, thyroid disorders
 - *Others*: Tumoral obstruction

Abbreviation: PAH, pulmonary arterial hypertension.

intimal hyperplasia, medial hypertrophy, adventitial proliferation, thrombus formation in the distal arterioles, inflammation and finally leading to plexiform arteriopathy.

There will be progressive increase of RV pressure overload leading to RV hypertrophy and dilatation. This afterload mismatch (maladaptation) in the right heart will eventually cause decompensated heart failure. The natural history of PAH with this presentation will have poor prognosis. The progressive increase in pulmonary vascular resistance (PVR) will have impact on the right atrial pressures, cardiac index. These three parameters are determinants of RV function. The RV is thinner than LV and the length of the LV is more than RV. The difference between both RV and LV is 3:1. The shape of the RV is complex in contrast to ellipsoidal shape of LV. The septum is concave toward LV in both systole and diastole. The volume of RV is larger than LV and RV mass is approximately one-sixth that of LV. The RV is mainly composed of superficial and deep muscle layers with different orientation. The arrangement of myofibers is different in RV. Heavily trabeculated RV wall is due to incompletely compacted endocardium. There will be changes in the adrenergic pathway of RV myocytes leading to reduced contractility. Hence, RV is more vulnerable for the stress and early failure is seen due to maladaptation.



Figures 1A to C (A) Normal distal pulmonary arteriole cross section; (B) Proliferation of smooth muscle cells and endothelial cells; (C) Complex vascular lesion: (a) normal distal pulmonary arteriole; (b) stage of vasoconstriction leading to smooth muscle hypertrophy and early intimal proliferation; (c) advanced vascular lesions producing adventitial and intimal proliferation and plexiform lesions

CLINICAL PRESENTATION

There should be high degree of clinical suspicion to diagnose PAH. This condition may mimic other pulmonary disorders. The diagnostic work-up should include a thorough clinical evaluation, laboratory evaluation including both noninvasive and invasive evaluation since IPAH is a diagnosis of exclusion (**Flow chart 1**).

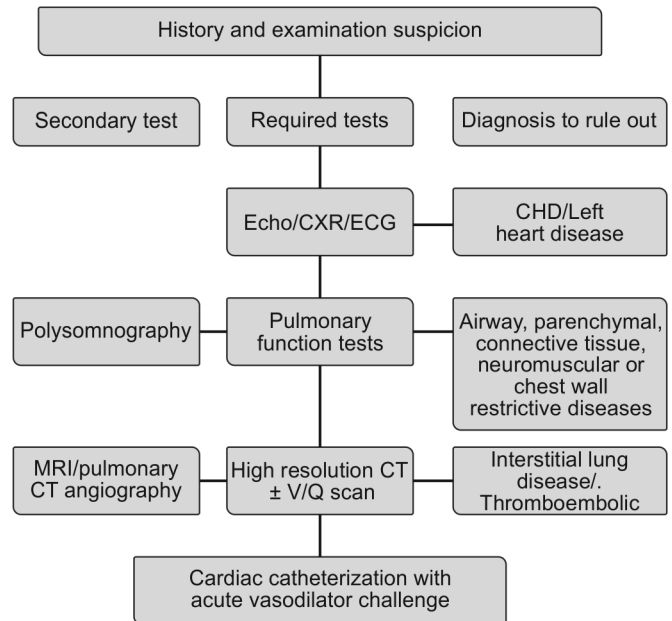
Most of the children present with nonspecific and atypical symptoms. Symptoms during exercise are common related to fixed cardiac output due to distal pulmonary vascular resistance. Breathlessness, easily fatigability and syncope are commonly noticed. Angina may be a rare symptom due to RV hypertrophy probably due to more myocardial demand. RV failure may produce symptoms like abdominal pain and distension due to hepatic congestion and stretching of the liver capsule. Physical signs include distended jugular veins with prominent *a* wave and subsequently *v* becomes taller due to development of RV dysfunction and tricuspid regurgitation. Cardiovascular examination generally shows parasternal heave, epigastric lift and cardiomegaly. The pulmonary component of second heart sound is loud and constant ejection click due to dilated pulmonary artery is usually appreciable. RV third heart sound generally suggests development of RV dysfunction. A pansystolic murmur of tricuspid regurgitation may be heard at the lower left sternal border and a diastolic murmur of pulmonary insufficiency is better appreciated during inspiration. Jaundice, edema and ascites are present in advanced stage of decompensated heart failure.

INVESTIGATIONS

Chest X-ray

The increase in cardiothoracic ratio is seen in latter part of the PAH. The RA and RV may be enlarged. The central pulmonary dilation with peripheral pruning is commonly noted (**Fig. 2**). Pulmonary arterial calcification is extremely rare and seen in secondary causes. Associated parenchymal changes are seen in lung disorders. Telltale evidence of past increased pulmonary blood flow may be seen in cases with congenital heart disease producing

Flow chart 1 Screening/diagnostic algorithm for pediatric PAH



Abbreviations: PAH, pulmonary arterial hypertension; Echo, echocardiogram; CXR, chest X-ray; ECG, electrocardiogram; CHD, congenital heart disease; MRI, magnetic resonance imaging; CT, computed tomography.

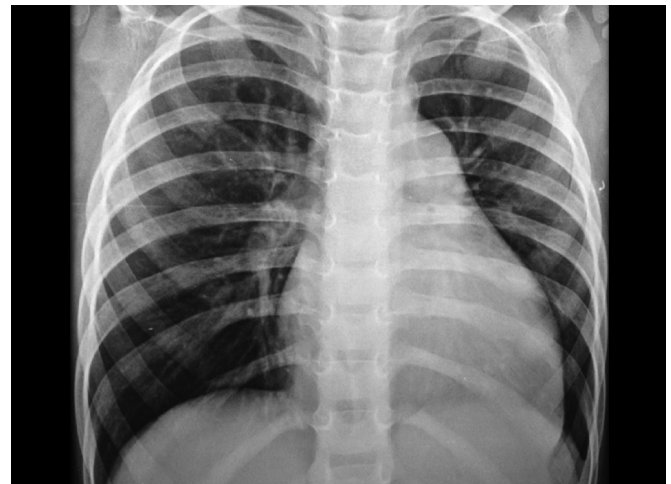


Figure 2 Chest X-ray of a child with pulmonary hypertension showing dilated central pulmonary arteries

PAH. Evidence of pulmonary venous hypertension gives clue to the diagnosis of left heart disease.

Electrocardiogram

Electrocardiogram (ECG) may provide clues to support the diagnosis of PAH. Right atrial enlargement, RV hypertrophy and right axis deviation are commonly seen (**Fig. 3**). Monophasic R in V1 and qR in V1 are generally suggestive of systemic or suprasystemic pulmonary artery pressures (PAPs). Arrhythmias are rare however, atrial arrhythmias include ectopic atrial rhythm, and flutter or fibrillation is common than ventricular arrhythmias.

Echocardiography (Figs 4A to D)

The assessment includes: (a) estimation of PAP, (b) assessment of RV function, and (c) assessment of severity of valvar regurgitations.

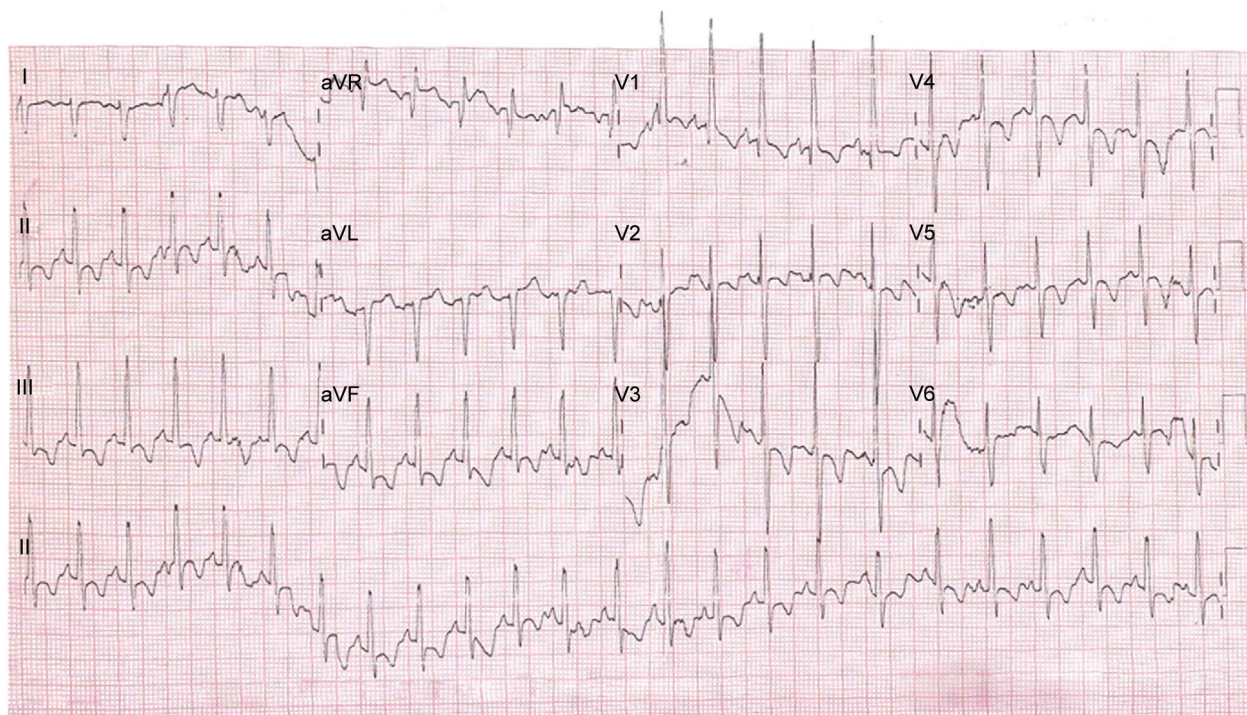


Figure 3 Electrocardiogram of a child with severe pulmonary hypertension showing right axis deviation and right ventricular hypertrophy as evidenced by tall R waves in V1

Estimation of Pulmonary Artery Pressure (PAP)

- This is based on the peak velocity of the jet of tricuspid regurgitation. The modified Bernoulli equation: $4v^2$ ($4 \times \text{TR velocity}$) + RA mean pressure. The PAP may be underestimated in case with RV dysfunction; hence, assessments of other parameters are helpful in diagnosis and estimation of severity of PAH.
 - Calculation of mean PAP from pulmonary regurgitation: mean PAP = $0.61 \times \text{PA systolic pressure} + 2 \text{ mm Hg}$.
- The right atrium, RV and pulmonary artery are dilated. Straightening of interventricular septum or D-shaped septum is seen in severe PAH. The LV function is usually preserved; however, size of the LV may be smaller in cases with suprasystemic PAH due to bowing of interventricular septum to LV.

Assessment of Right Ventricular Function

Quantitative assessment of RV function is quite challenging due to geometry of the RV. Several parameters are available for the assessment of RV function but none is accurate.

- Tei index (myocardial performance index)** The myocardial performance index is the ratio of isovolumic time intervals to ventricular ejection time. This index is independent of preload, afterload and heart rate. The normal value is 0.28 ± 0.04 and increases in the presence of RV dysfunction.
- Tricuspid annular plane systolic excursion (TAPSE)** This is a measure of longitudinal function of RV and measured from the tricuspid lateral annulus. TAPSE less than 16 mm indicates RV systolic dysfunction.
- RV ejection fraction (RVEF)** RVEF is highly dependent on loading conditions and may not reflect actual contractility. The normal range varies between 40% and 76%. Magnetic resonance imaging is the most accurate method to assess RVEF.

- RV fractional area** Two-dimensional area less than 35% indicates RV systolic dysfunction.

MRI and High Resolution CT Scans

High-resolution computed tomography (HRCT) is useful in diagnosing parenchymal lung disease and pulmonary veno-occlusive disease or isolated pulmonary vein obstruction (**Fig. 5**).

Pulmonary Function Tests

Airway diseases and other lung parenchymal diseases can be assessed by pulmonary function tests (PFT).

Six-minute Walk Test

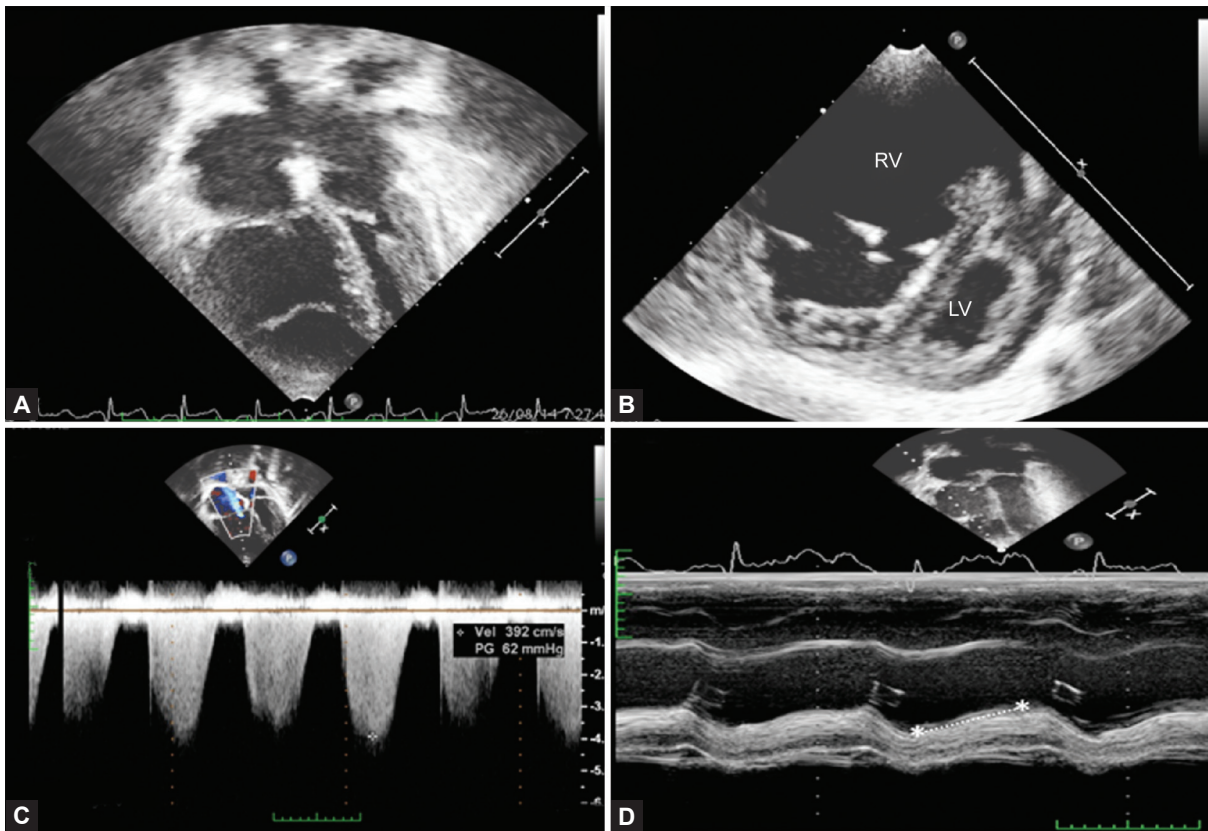
Six-minute walk test is a useful in assessing functional capacity of the patient. It is a good clinical test to see the treatment response during follow-up assessment. A walking distance of greater than 380 m during treatment suggests good response whereas less than 330 m suggests impaired prognosis.

Ventilation-perfusion Scintigraphy

This is a good screening test to rule out pulmonary thromboembolism. Coagulation disorders, elderly, patients with deep vein thrombosis and on oral contraceptive people are at high risk for pulmonary thromboembolism. VQ mismatch and multiple perfusion defects are generally seen in chronic pulmonary thromboembolism.

Laboratory Investigations

Routine complete blood picture, liver function test as a baseline in case of right heart failure or prior to the starting of endothelin receptor antagonists or phosphodiesterase-5 inhibitors is mandatory. Other necessary laboratory tests are indicated based on the clinical suspicion of other diseases.



Figures 4A to D Transthoracic echocardiogram showing: (A) Dilated right heart in apical four-chambered view; (B) D-shaped left ventricle (LV) and dilated right ventricle (RV); (C) RV systolic pressure by tricuspid velocity jet showing severe pulmonary hypertension; (D) Tricuspid annular plane systolic excursion (TAPSE) by M-mode showing significantly reduced suggestive of RV dysfunction

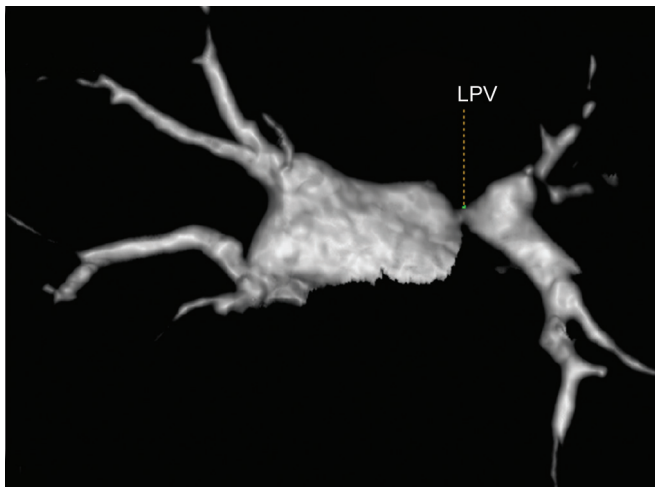


Figure 5 Computerized tomography angiogram showing left pulmonary venous (LPV) obstruction in a child with pulmonary hypertension

Cardiac Catheterization

A routine diagnostic cardiac catheterization is not indicated since the subset of population is sick and high-risk for sudden cardiac death during cardiac catheterization. Good patient preparation and control of heart failure prior to the vasodilator response test in the catheterization laboratory reduce the risk of complications.

The right heart study includes assessment of cardiac output and estimation of pulmonary vascular resistance.

MANAGEMENT

The use of newer medications modified the prognosis in recent times. Aggressive use of PAH targeted therapy has significantly changed the outcome and symptomatic status (**Flow chart 2**).

General Measures

Physical exercise should be avoided even in asymptomatic patients since exercise cardiac output can not be maintained. High altitudes should be avoided above 1,500 m of sea level and necessarily should be supplemented with oxygen. All respiratory infections should be treated promptly since significant mortality is associated with pneumonia. Vaccination against influenza and pneumococcal should be considered.

Supportive Treatment

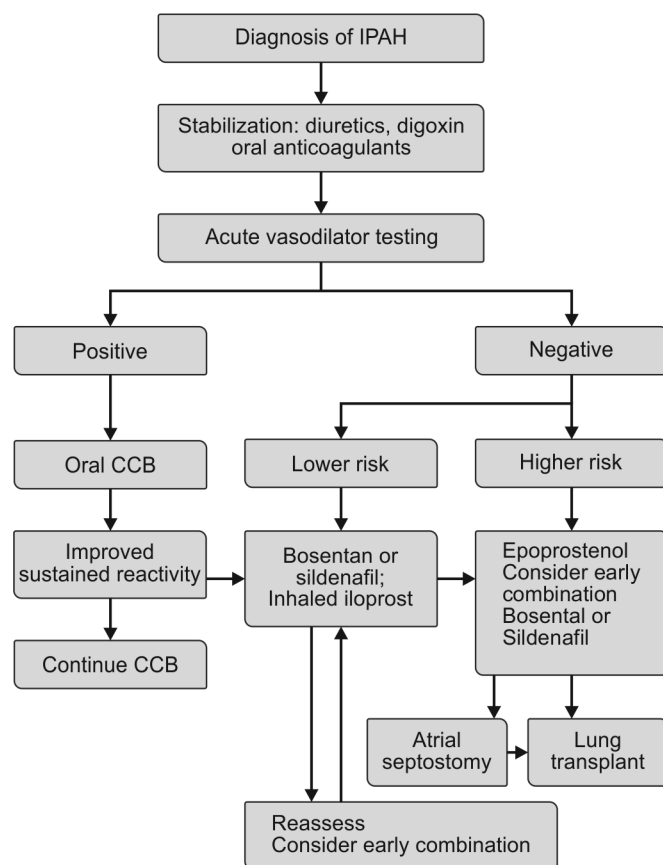
Diuretics

Diuretics should be considered in cases with decompensated heart failure and RV dysfunction. Care should be taken not to deplete the intravascular volume since cardiac output is predominantly preload dependent in the right side. Combination of furosemide and spironolactone are usually recommended.

Digoxin

Impaired RV function is generally seen in the later part of the PAH. Inotropic support may be helpful to some extent in the advanced

Flow chart 2 Treatment algorithm for the management of pediatric idiopathic pulmonary arterial hypertension (IPAH)



Abbreviations: CCB, calcium channel blockers; IPAH, idiopathic pulmonary arterial hypertension.

cases. Digoxin may also be indicated in case of supraventricular tachyarrhythmia to slow the ventricular rate.

Oral Anticoagulants

Although there is no definitive data to suggest the beneficial effects, Warfarin has been shown to be associated with improved survival. Oral anticoagulant (OAC) may prevent secondary thrombosis in the pulmonary arteries with low pulmonary blood flow due to high pulmonary vascular disease. The international normalization ratio (INR) may be adjusted to minimal range between 1.3 and 1.5.

Targeted Specific Treatment

Calcium Channel Blockers

Nearly 10% of the patients with PAH show response to acute vasodilator testing in the catheterization. The vasodilator testing can be performed using intravenous epoprostenol, adenosine or inhaled nitric oxide (NO). A decrease in pulmonary artery pressure of greater than 20% or pulmonary vascular resistance greater than 30% is usually considered as positive response and beneficial from long-term calcium channel blocker treatment. Either amlodipine or nifedipine or diltiazem has been used. These medications should be avoided in children less than 1 year of age due to negative inotropic effect.

Prostanoids

Intravenous epoprostenol It has been shown improved survival in patients with PAH. The medication is expensive and hence limits its usage in India. The medication is delivered by infusion pumps through long peripherally inserted central catheters. The starting dose is 2–4 ng/kg/min and increased to target dose of 10–15 ng/kg/min for 2–4 weeks. The side effects include headache, flushing, diarrhea, nausea and vomiting.

Iloprost An inhaled prostacyclin analog with half-life of 20–25 min has shown beneficial effects on symptomatology and quality of life. The major advantage is its selective nature on pulmonary vasodilatation and less effect on the systemic blood pressure.

Beraprost This is an orally available prostacyclin analog. The medication is not available in USA and India due to its inconsistent results in two different clinical trials.

Endothelin Receptor Antagonists

Endothelin receptors exist in two isoforms, ET_A and ET_B. Smooth muscle cells are responsible for vasoconstriction due to ET_A receptors. The ET_B receptors mediate endothelium-dependent vascular relaxation by inducing NO and prostacyclin release. This induces vasodilatation. Bosentan is a dual endothelial receptor antagonist and has been studied in patients with PAH. Two randomized double-blind, placebo-controlled studies showed improvement of six-minute walk test, symptomatic status and reduction in mortality. The suggested dosage was 31.25 mg between 10 kg and 20 kg, 62.5 mg between 20 kg and 40 kg and 125 mg for more than 40 kg. In FUTURE-1 study, bosentan dose was 2 mg/kg twice daily in the first 4 weeks and the 4 mg/kg twice daily for 8 weeks. Bosentan is metabolized in the liver and hence assessment of liver functions baseline and periodically every 4–6 weeks is mandatory.

Phosphodiesterase-5 Inhibitors

Increase concentration of cGMP in the smooth muscles of the pulmonary vessels produces smooth muscle relaxation and subsequently pulmonary vasodilatation. Sildenafil is a selective inhibitor of cGMP phosphodiesterase type 5, leading to increase cGMP in the pulmonary vasculature. Sildenafil can be used in children with PAH in the dose of 0.5–1 mg/kg/dose for three to four times a day. The main side effects are erections and systemic hypotension when high doses are used. Tadalafil is another phosphodiesterase-5 inhibitor and can be used once in a day; however, its usage in pediatric population has not been established.

Combination Therapy

A combination of two or more drugs appears to be reasonable since there are three different intracellular pathways that include: (i) NO, (ii) prostacyclin and (iii) endothelin. It is probably safer to start with one medication and second drug may be started based on the response. The combination of sildenafil and inhaled iloprost appears more potent.

Other Procedures

Balloon atrial septostomy The natural history of Eisenmenger syndrome appears to be better than IPAH. Blade balloon atrial septostomy allows right to left shunt at atrial level and decompresses right atrium and RV with improvement of clinical signs and symptoms of right heart failure.

Lung transplantation Lung transplantation is indicated in selected cases of advanced heart failure. The availability of donor, technical difficulties and allograft rejection limit the therapy even in western countries.

PROGNOSIS AND SURVIVAL

Netherlands Registry

The yearly incidence of PAH was 63.7 cases per million children. The annual incidence of IPAH and PAH due to congenital heart disease was 0.7 and 2.2 cases per million respectively. The estimated median survival of children was 4.12 years prior to the availability of targeted treatment. With the available pulmonary vasodilators, the survival rate has been shown somewhat improvement. The REVEAL registry showed 1-, 3- and 5-year estimated survival rates of $94 \pm 4\%$, $84 \pm 5\%$ and $74 \pm 6\%$, respectively. Poor prognostic factors include: history of syncope, clinical heart failure, failure to thrive, > Class III, pericardial effusion, right heart dysfunction, elevated brain natriuretic peptide (BNP), right atrial mean pressure greater than 10 mm Hg and pulmonary vascular resistance index (PVRI) greater than 20.

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IN A NUTSHELL

1. Pulmonary hypertension (PAH) is defined as mean pulmonary arterial pressures more than 25 mm Hg at rest or more than 30 mm Hg during exercise. Neonates and infants below 3 months of age are excluded in the definition.
2. PAH may be idiopathic or secondary.
3. PAH secondary to congenital and other structural or systemic disease is still one of the leading causes globally.
4. The etiology of IPAH is unknown and poorly understood.
5. The diagnosis is by exclusion after complete evaluation to rule out secondary causes.
6. The natural history of IPAH appears to be still guarded with overall median survival of only 10 months.

Chapter 40.29

Acute Rheumatic Fever

B Anjaiah

Acute rheumatic fever is an inflammatory autoimmune disorder that affects several organs of the body characterized by arthritis, carditis, chorea, rheumatic nodules, erythema marginatum and fever caused by group A β -hemolytic *Streptococcus* (GABHS).

ETIOLOGY

Acute rheumatic fever is exclusively caused by GABHS, a gram-positive organism. Lancefield classified group A β -hemolytic streptococci into serologic types on the basis of the M protein. The M protein is the most important because it determines the virulence of the organism, stimulates the formation of opsonizing and precipitating antibodies. Serotypes such as M types 1, 3, 5, 6, 14, 18 and 24 have been associated with rheumatic fever. Group C and G streptococci may also contribute to acute rheumatic fever.

EPIDEMIOLOGY

Geographical Distribution

The incidence of acute rheumatic fever is more common in countries with tropical climate, particularly in developing countries. There is a decline in the incidence of acute rheumatic fever in industrialized countries, but its prevalence in developing countries of the world was very high. More than 80% of the world's cases of acute rheumatic fever and rheumatic heart disease (RHD) occur in people living in developing countries. The reasons are poverty, unhygienic environments, lack of accessibility to medical care and household overcrowding. Recently, the prevalence of rheumatic fever has shown a steep decline in Indian settings.

Incidence

The incidence of acute rheumatic fever varies with geographic location and the population ranges from 3 to 61 per 100,000 school children. The incidence of rheumatic fever in Indian children by echo studies is 0.5–11 per 1,000.

Sociodemographic Characteristics

The vulnerable age group for development of acute rheumatic fever is 5–15 years, but it is rare below 4 years of age. There is no difference in the incidence of acute rheumatic fever between males and females, but the incidence of chorea and RHD are more in females. Acute rheumatic fever is most common during winter and spring, a seasonal variation similar to that of streptococcal pharyngitis. The incidence of initial attacks of acute rheumatic fever is more in disadvantaged population, presumably because crowded living conditions that facilitate the spread of streptococcal infection.

Genetics

Genetic predisposition of individual plays an important role in pathogenesis of the disease. DR4 allele is found in Indian, American Caucasian and Saudi-Arabian patients. DR7 is found in Brazil and Turkey.

PATHOGENESIS

Pathogenesis of relationship between acute rheumatic fever and group A β -hemolytic streptococcal infection is not clear. Acute rheumatic fever is supposed to be an autoimmune disease in which invasive streptococcal infection evokes an antibody response from

the host and this antibody attacks antigenically similar host tissues (**Flow chart 1**). Four streptococcal host cross-reactive antigen-antibody systems have been identified.

1. Cardiac myofibrillar smooth muscle antigen cross-reacting with streptococcal cell wall and cell membrane antigen.
2. Heart valve fibroblast antigen cross-reacting with streptococcal cell membrane antigen.
3. Subthalamic and caudate nuclei antigen cross-reacting with streptococcal cell membrane antigen.
4. Heart valve and connective tissue antigen cross-reacting with streptococcal group A carbohydrate antigen.

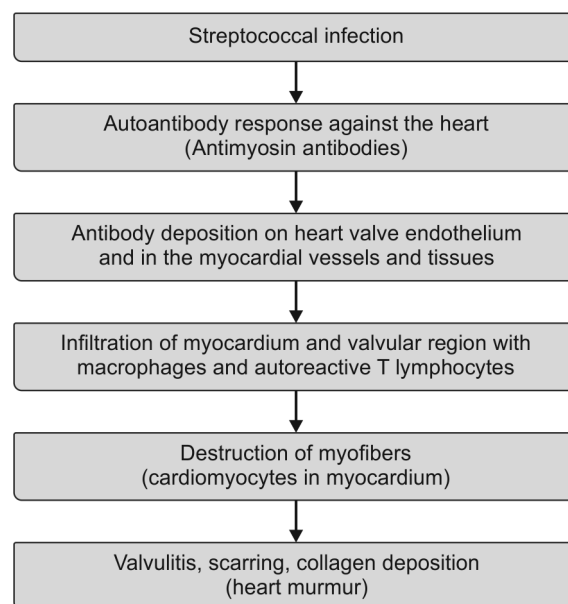
It is also possible that streptococcal extracellular products play a role in the pathogenesis of acute rheumatic fever.

PATHOLOGY

In acute rheumatic fever, immunological events cause proliferative and exudative inflammatory reactions in the connective tissues of the affected organs. These lesions are more distinctive within the heart but also involve joints, subcutaneous tissues, brain and vessels of the lung. The pathological hallmark of rheumatic carditis is pancarditis involving pericardium, myocardium and endocardium. The histopathological hallmark of carditis is the presence of Aschoff body in the interstitium. Pericarditis is characterized by the deposition of a serofibrinous exudate, giving the so-called bread-and-butter appearance. It heals with no significant adhesions and constriction. The ventricles and atria are often enlarged. Myocardium is edematous and shows nonspecific inflammation. There is no evidence of cell damage. Myocardium is infiltrated with lymphocytes, macrophages and other inflammatory cells. Endocardial inflammatory changes are responsible for the valvulitis. Small, 1–2 mm, friable, fibrinous, verrucous vegetations may occur on the atrial surface of the mitral valves or on the ventricle side of the aortic valves or at sites of valve closure. It is infiltrated with histiocytes and lymphocytes. It may result in mitral stenosis (MS), mitral regurgitation (MR) or aortic regurgitation (AR). There is a fibrotic thickening of the posterior left atrial wall called *McCallum's Patch*.

Generalized vasculitis involving coronary arteries and the aorta can be seen. Histology of subcutaneous nodules reveals

Flow chart 1 Hypothesis of the immunopathogenesis of acute rheumatic fever



central fibrinoid necrosis surrounded by histiocytes, fibroblasts, occasionally lymphocytes and rarely polymorphs.

CLINICAL FEATURES

Arthritis, carditis, chorea, subcutaneous nodules and erythema marginatum constitute the major manifestations of acute rheumatic fever. Arthritis, carditis and erythema marginatum are the acute major manifestations whereas subcutaneous nodules and chorea are the late manifestations. A patient may present with one, two or more of these manifestations with varying severity. The minor manifestations are fever, arthralgia, abdominal pain, abnormal acute phase reactants and prolonged PR interval.

Polyarthritis

Arthritis occurs in 40–70% of patients of acute rheumatic fever. It is one of the major manifestations of acute rheumatic fever. Major joints like knees, ankles, wrists and elbows are commonly involved. Rarely, small joints like metacarpophalangeal, spine and temporomandibular may be involved. The arthritis of acute rheumatic fever is characteristically migratory and fleeting. The joints are swollen, hot, red and tender. The pain moves from one joint to the other over a period of hours. The duration of arthritis is 2–4 weeks and spontaneous resolution occurs without residual defects exception being Jaccoud's arthritis in which there is an erosion of the metacarpal heads resulting in hook-like deformities which is extremely rare. Arthralgia without joint involvement usually affects large joints in the same migratory pattern.

Carditis

Cardiac inflammation develops in 50% of the patients. High frequency of this manifestation develops in developing countries. Pancarditis is the hallmark of rheumatic carditis (**Table 1**). Carditis is the most common cause of morbidity and mortality with varied manifestations. It may be associated with other manifestations like arthritis, subcutaneous nodules, etc., in some patients it may be subtle. RHD occurs at a much younger age in India as compared to Western countries and structural stenosis or incompetence of the mitral valve occurs very frequently in young children. Juvenile MS has been reported from all developing countries and its mechanism is not known.

Mitral valve involvement presenting as MR occurs in 92–95% of patients with carditis. Mitral valve involvement is observed in 70–75% of patients with endocarditis. Aortic valve involvement in rheumatic carditis presents as AR occurs in 20–25% of patients and it is an isolated finding in 5–8%. Tricuspid valve involvement is seen in 30–50% of patients. Involvement of pulmonary valve is rare. Pericarditis occurs in approximately 4–11% of patients with acute rheumatic carditis.

Table 1 Clinical features of acute pancarditis in acute rheumatic fever

Involvement	Clinical features
Pericarditis	<ul style="list-style-type: none"> • Precordial chest pain • Friction rub • Effusion
Myocarditis	<ul style="list-style-type: none"> • Cardiomegaly • Tachycardia • Congestive heart failure • Soft first heart sound • S₃ gallop
Endocarditis	<ul style="list-style-type: none"> • Apical pansystolic murmur • Apical mid-diastolic murmur (Carey Coombs murmur) • Basal early diastolic murmur

Subclinical (Silent) Carditis

There is an entity called subclinical carditis in which silent carditis is found in patients with isolated arthritis and/or pure chorea, without auscultatory findings of valvar dysfunction. There is a pathological pattern of valvar regurgitation and thickening of the valvar leaflets revealed by Doppler echocardiography. Mild degrees of MR and/or AR are most commonly described in rheumatic subclinical carditis. These patients require secondary prophylaxis treatment to prevent progression of the valvar lesion.

Chronic Rheumatic Fever

In most attacks of acute rheumatic fever, clinical and laboratory evidence of inflammatory activity usually subside within 6 months. In some patients, evidence of rheumatic activity persists for a much longer time without recurrent streptococcal infection. A long duration was defined as an inflammation lasting for more than 223 days termed as *chronic RF*. There is a clinical activity of arthritis or arthralgia and tachycardia.

Subcutaneous Nodules

Subcutaneous nodules occur as painless, small (0.5–2 cm), mobile lumps beneath the skin overlying bony prominences such as ulnar borders of forearms, knuckles, shin of tibia, occipital region (**Fig. 1**) and spinal process of vertebrae. They are a delayed manifestation of rheumatic fever and appear around 6 weeks after the onset of rheumatic fever. They are associated with severe carditis. These occur in 0–10% of the patients of acute rheumatic fever and sometimes it may be an isolated major manifestation. Spontaneous resolution occurs in 2–3 weeks without residual lesions.

Erythema Marginatum

These occur in 5% of patients. It is uncommon in Indian reports of children with acute rheumatic fever probably because the evanescent lesion might not be recognized because of the brown or dark skin color of our population or might not be appreciated as important to seek medical attention by their parents. It is associated with carditis and subcutaneous nodules. It appears only in patients with carditis. If present, it is virtually a sign of rheumatic fever.

Sydenham Chorea (St. Vitus Dance)

The incidence of Sydenham chorea in children with acute rheumatic fever is less than 15%. There is an inflammatory involvement of subthalamic and caudate nuclei of central nervous system. It is a delayed manifestation (1–7 months) of rheumatic fever which has a female predilection and increases after puberty. The important features are involuntary movements which are abrupt, sudden,

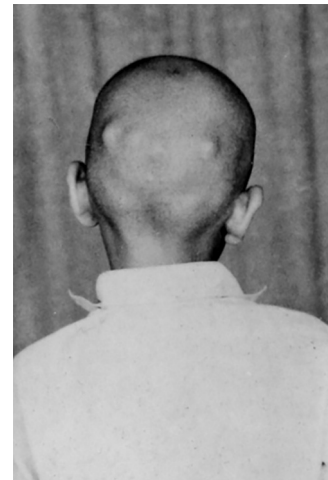


Figure 1 A boy with occipital subcutaneous nodules

quasi-purposive, nonrepetitive and jerky movements, hypotonia and muscle weakness mainly involving the distal parts of the body and emotional instability. The important signs are darting tongue or jack-in-the box tongue or snake tongue flicks, hyperpronation of the raised hands, choreic hand in the extended hands, milkmaid grip and dancing gait (**Figs 2A and B**). It can be associated with carditis but not with arthritis. Hemichorea and chorea gravidarum are known variants.

Other Manifestations

Fever is seen in early stages of acute rheumatic fever and lasts usually for less than 2 weeks and rarely exceeds beyond 39°C. Anemia, epistaxis, weight loss and pallor are the other manifestations. Abdominal pain can be due to nonspecific mesenteric adenitis or due to congestive hepatomegaly. Only arthralgia can be there; joint pain involves large joints, asymmetrical, migratory, rarely incapacitates and lasts less than 2 weeks. There is a high correlation with severe carditis.

Table 2 lists the diseases to be considered in the differential diagnosis of acute rheumatic fever.

DIAGNOSIS

The diagnosis of acute rheumatic fever is considered on the basis of WHO adoption of (2004) revised Jones criteria, 1992 (**Tables 3 and 4**) and ancillary studies.

Ancillary Studies

Studies to Support Recent Group A β -Streptococcal Infection

- Increasing antistreptolysin O (ASO) titer from the end of 1 week and reaching the peak level by 3–6 weeks following infection. In children, 1:333 and in adults 1:250 are often considered as significant titer indicative of recent group A β -streptococcal (GABS) infection.
- Anti-DNase B titers rise 1–2 weeks of infection and reach the peak levels 6–8 weeks after infection.
- Culture of the organisms from throat is also important.

Tests to Support Inflammatory Process

- Erythrocyte sedimentation rate (ESR):** There is an increase in plasma fibrinogen secondary to inflammation causing an elevated ESR.
- C-reactive protein (CRP):** It is elevated promptly in inflammatory process and is not affected by congestive heart failure (CHF).



Figures 2A and B Signs of rheumatic chorea. (A) A girl with choreic posturing; (B) Hyperpronation of the raised hands

Table 2 Differential diagnosis of acute rheumatic fever

Arthritis	Carditis	Chorea
Rheumatoid arthritis	Kawasaki disease	Huntington chorea
Systemic lupus erythematosus	Viral myocarditis	Wilson disease
Serum sickness	Viral pericarditis	Systemic lupus erythematosus (SLE)
Sickle cell disease	Congenital heart disease	Tics
Postinfective reactive arthritis	Innocent murmur	Hyperactivity
(<i>Shigella</i> , <i>Salmonella</i> , <i>Yersinia</i>)		
Leukemia		

Table 3 WHO adoption of (2004) revised Jones criteria of 1992

Clinical and laboratory criteria	Supportive evidence of preceding streptococcal infection
Major criteria (more specific) <ul style="list-style-type: none"> • Polyarthritis • Carditis • Chorea • Subcutaneous nodules • Erythema marginatum Minor criteria (less specific) <ul style="list-style-type: none"> • Fever • Polyarthralgia • ESR, CRP, leukocytosis • ECG: prolonged PR interval 	<ul style="list-style-type: none"> • ASO • Antideoxyribonuclease • History of (within previous 45 days) streptococcal sore throat • Scarlet fever • Positive throat culture • Positive rapid streptococcal antigen detection test

Abbreviations: ASO, antistreptolysin O; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; ECG, electrocardiogram.

Table 4 WHO criteria for diagnosis of acute rheumatic fever and rheumatic heart disease

S. No.	Diagnostic categories	Criteria
1.	Primary episode of rheumatic fever	Two major or one major and two minor manifestations plus evidence of a preceding GABS infection, streptococcal infection
2.	Recurrent attacks of rheumatic fever in a patient without established rheumatic heart disease	As for a primary episode of rheumatic fever
3.	Recurrent attack of rheumatic fever in a patient with established rheumatic heart disease	Two minor manifestations plus evidence of a preceding group A streptococcal infection
4.	Rheumatic chorea	Other major manifestations or evidence of group A streptococcal infections are not required because these are delayed manifestations of streptococcal infection
5.	Insidious onset of rheumatic carditis. Chronic valve lesions of rheumatic heart disease, i.e., patients presenting for the first time with pure MS or mixed mitral valve disease with or without aortic valve disease	Do not require any other criteria to be diagnosed as having rheumatic heart disease

Abbreviations: GABS, group A β -streptococcal; MS, mitral stenosis.

Tests Suggestive of Pancarditis

- X-ray chest to identify the cardiac enlargement and congestion of the lungs in carditis.
- *Electrocardiography for presence of any of the following findings:* (a) sinus tachycardia, (b) prolonged PR interval and (c) ST segment and T-wave changes of acute pericarditis.
- *Echocardiography:* Two dimensional echocardiography is central to the diagnosis and should be performed in all patients of acute or chronic RHD. It can identify pericarditis with pericardial effusion, myocarditis, enlargement of cardiac chambers and involvement of mitral valves, aortic valves, and right sided valves which may manifest as regurgitation.
- *Cardiac catheterization:* Cardiac catheterization and angiography are rarely necessary for the management of patients with acute rheumatic valvar disease.

MANAGEMENT

All children with suspected carditis in acute rheumatic fever need to be admitted, investigated, monitored and treated appropriately as the carditis is getting confirmed.

Antibiotic Therapy

Once the diagnosis of acute rheumatic fever has been established, the affected children must be given 10 days of orally administered penicillin or erythromycin or a single intramuscular injection of benzathine penicillin regardless of the throat culture results to eradicate GABS from the upper respiratory tract. After this initial course of antibiotic therapy, they will be started on long-term antibiotic prophylaxis.

Anti-inflammatory treatment is summarized in **Table 5**.

Rest and Ambulation

Rest and graded ambulation is suggested as per the severity of the lesion. They are allowed to ambulate as soon as the signs of acute inflammation have subsided. Patients with carditis require longer periods of bed rest.

COURSE AND PROGNOSIS

In 1884, Lasague noted that *rheumatic fever* is a disease that *licks the joints and bites the heart*. The sequelae depend upon the severity of involvement of the heart. Arthritis and chorea have good prognosis. If carditis is limited to systolic murmur, only 25% of patients are left with residual heart disease. The patient with congestive cardiac failure develops chronic valvar heart disease over a period of 5–10 years. Death during acute attack is rare in the past 30 years due to availability of better awareness and seeking early treatment facilities

Table 5 Treatment of acute rheumatic fever

Clinical condition	Anti-inflammatory drug
Arthralgia	Any analgesic can be used
Arthritis	Aspirin 100 mg/kg/day in divided doses for 2 weeks followed by 75 mg/kg/day in divided doses for 4–6 weeks
Carditis with cardiomegaly or CHF	Prednisolone 2 mg/kg/day in divided doses for 2 weeks and taper to stop it in another 2 weeks. At the time of tapering of corticosteroids introduce aspirin 75 mg/kg/day in divided doses for 4–6 weeks to prevent rebound phenomena
CHF	<i>Antifailure measures:</i> Bed rest, diuretics, digoxin, salt-restricted diet
Chorea	Sodium valproate, haloperidol can be given

Abbreviation: CHF, congestive heart failure.

in a hospital. Average attack of acute rheumatic fever lasts for about 12 weeks. However, it may be prolonged even up to 6 months especially with carditis or chorea. If rheumatic fever is active for more than 6 months, it can be classified as *chronic rheumatic fever*.

PROPHYLAXIS

Primary Prevention

Antibiotic therapy is effective in eradicating GABHS upper respiratory infection if started within 9 days after onset of symptoms to prevent rheumatic fever, particularly carditis (**Table 6**).

Secondary Prophylaxis

The incidence of recurrence of acute rheumatic fever is more in developing countries and adherence to penicillin prophylaxis is the key against recurrence of acute rheumatic fever and consequent worsening of RHD. Secondary prophylaxis reduces severity and is associated with improvement in heart disease in about 50–70% cases. Secondary prevention is a proven, simple and cost-effective strategy for controlling RHD (**Table 7**). Duration of secondary prophylaxis depends on the presence of carditis during the acute episode: No carditis—prophylaxis for 5 years after last attack or 18 years of age (whichever is longer). Patients with residual heart disease will require lifelong prophylaxis.

Antistreptococcal Vaccine

A GABHS vaccine would prevent acute rheumatic fever and RHD by preventing antecedent GABHS infection. A multivalent M type specific vaccine has completed phase 2 trials in adults with evidence of safety and immunogenicity.

MORE ON THIS TOPIC

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Table 6 Primary prophylaxis for rheumatic fever
(Treatment of streptococcal tonsillopharyngitis)

Antibiotic	Mode	Dose	Duration
Benzathine penicillin	Intramuscular	< 27 kg: 6 lac units > 27 kg: 12 lac units	Single dose
Phenoxymethylpenicillin (penicillin V)	Orally 2–4 times/day	Children: 250–500 mg Adults: 250 mg or 500 mg	10 days
Amoxicillin	Orally 2–3 times/day	25–50 mg/kg/day Adult dose: 750–1,500 mg/day	10 days
First generation cephalosporin	Orally 2–3 times/day	Varies with agent	10 days
Erythromycin ethyl succinate	Orally 4 times/day	40 mg/kg/day	10 days

(Adapted from WHO Technical Report Series 2004)

Table 7 Drugs used in secondary prophylaxis for rheumatic fever

Drugs	Dose	Route	Frequency
Benzathine penicillin (benzathine penicillin G)	600,000 units for patients < 27 kg 1,200,000 units for patients ≥ 27 kg	Intramuscular	Every 3–4 weeks
Or			
Phenoxymethylpenicillin (penicillin V)	250 mg	Oral	Twice daily
<i>Patients allergic to penicillin</i>			
Sulfadiazine	0.5 g for patients < 27 kg 1.0 g for patients ≥ 27 kg	Oral	Once daily
<i>Patients allergic to penicillin and sulfadiazine</i>			
Erythromycin	250 mg	Oral	Twice daily

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IN A NUTSHELL

1. Acute rheumatic fever is an inflammatory autoimmune disorder that affects several organs of the body characterized by arthritis, carditis, chorea, rheumatic nodules, erythema marginatum and fever caused by GABHS.
2. Peak incidence is between ages 5 and 15 years.
3. Diagnosis is based on Jones criteria and confirmation of streptococcal infection.
4. Carditis is the major cause of morbidity and mortality and is the leading cause of valvular involvement. Mitral and aortic valves are mostly involved.
5. Acute rheumatic fever is treated with aspirin and/or steroids depending on the presence of carditis.
6. Primary prevention consists of appropriate treatment of all episodes of streptococcal sore throat.
7. Children with residual heart disease require lifelong prophylaxis with penicillin.

Chapter 40.30

Rheumatic Heart Disease and Lesions of the Mitral Valve

R Krishna Kumar

Rheumatic heart disease (RHD) is the only long-term sequelae of acute rheumatic fever (RF), a nonsuppurative immune-mediated complication of group A streptococcal pharyngeal infection. RHD, now a rarity in developed nations, still remains a major public health problem in regions with low human development indices.

The mitral valve (MV) is the most frequently affected and maximally damaged structure in children with RHD. In endemic regions with high disease burden, the initial episodes tend to occur at a very young age and are frequently associated with carditis, often severe. Recurrences are common. Advanced heart valve scarring is seen at a young age. Juvenile rheumatic MV stenosis is a well-recognized example that is almost exclusively seen in regions with a high incidence of RF. The involvement of the MV is in the form of either mitral stenosis (MS) or mitral regurgitation (MR) or, not uncommonly, a combination of the two.

A clear understanding of facts and familiarity with all the facets of RF and RHD is still very essential to all pediatricians in India and other developing nations, in spite of a perceptible decline in its incidence. This chapter aims to fulfill the above-mentioned objectives by providing a broad background information regarding basics of rheumatic valvar heart disease with greater focus and emphasis on MV disease.

EPIDEMIOLOGY

Improving living standards, e.g., reduction in overcrowding, improved public hygiene, better access to health care and use of antibiotics for prompt treatment of streptococcal infections in industrialized nations around the world brought about a sharp decline in acute RF and RHD. Interestingly, the decline started even decades before the introduction of penicillin. Industrialized nations now have an average annual RF incidence of less than 0.5 per 100,000 and RHD prevalence of less than 0.05 per 1,000.

In many parts of the developing world, RF and RHD continue unabated like many other infectious diseases, largely reflecting the relatively poor living standards and healthcare availability. The prevalence of RHD in school age children has varied from 0.4 to 21 per 1,000 children in various series from developing countries. RHD being held responsible for one in every 150 deaths and more than 300,000 deaths a year in developing nations remain a major public health burden.

Prevalence estimation of RHD among children has often been done by school surveys in the region, where invariably school enrollment rates were likely to be low. Population-based registries have the potential to capture all age groups, but are heavily dependent on referral mechanisms. Hospital-based statistics selectively report the most seriously affected patients. Recent large studies have used echocardiography in population-based surveys and suggest a much higher prevalence of RHD in children from endemic regions. Most of the cases identified through echocardiography are clinically silent and their natural history is not known at this time. It is also not clear whether penicillin prophylaxis is warranted for clinically silent RHD, although most investigators have chosen to recommend it.

PATHOGENESIS

After an episode of RF with pancarditis, permanent damage is seen affecting only the heart valves whereas all other affected tissues typically heal with no residual sequelae, e.g., complete resolution of other major tissue lesions such as arthritis, chorea, subcutaneous nodules and pericarditis.

The immunopathological findings suggest that RF predominantly damages the vascular endothelium and mesothelium; the adjacent subendothelial and submesothelial tissues get involved to a certain depth. A new endothelium replaces the damaged endothelium within days after injury without significant scarring. The valves are structurally vulnerable for damage in having a small core of connective tissue covered by two layers of endothelium with a predisposition for permanent scarring.

The initial damage in the endothelium is initiated by a humoral immune response, resulting in vascular cell adhesion molecule-1 (VCAM-1) being expressed on the endothelium. Activation of cellular immune response soon follows resulting in attachment of CD4⁺, CD8⁺ T lymphocytes and macrophages to the valvar endothelium and migration to the core of connective tissue. They trigger inflammatory response resulting in neovascularization of the valve substance. The endothelium of the newly formed vessels may serve as a substrate for additional inflammation and perhaps set up a vicious cycle of inflammation, neovascularization and further damage resulting eventually in a permanently scarred valve.

PATHOLOGY

Autopsies of patients dying of RHD revealed that the MV was most commonly afflicted either alone or in combination with aortic valve (AV) and tricuspid valve (TV) (in 31.6% and 52.8% respectively). Organic involvement of the TV was documented in 38.4% of cases. The extent and severity of the disease process was most marked in MV, followed by AV and TV. Involvement of pulmonary valve (PV) is exceptional and is almost always associated with involvement of all valves. MR is the most common lesion encountered in adolescents and children. Other differences in manifestations of RHD between adults and children are listed in **Table 1**.

The well characterized pathologic gross features of RHD from autopsy studies are now well demonstrated through cross sectional [two-dimensional (2-D)] and more recently, through three-dimensional (3-D) echocardiography. **Table 2** lists all the pathologic features of RHD with their echocardiographic correlates.

CLINICAL FEATURES OF RHEUMATIC HEART VALVE DISEASE

A history of acute RF should be diligently sought while evaluating any child with symptoms suggestive of RHD. In many patients with RHD, such a history of episodes of acute RF may not be obtained. Not all episodes of RF may be severe enough to warrant medical attention. Episodes of RF may not be distinguished from other common febrile conditions encountered in childhood especially in the absence of arthritis. The ability of family members to clearly recall a history of RF may also be influenced by their socioeconomic and cultural background. In general, however, families of children who have established RHD at a young age often recall the episode.

A diagnosis of rheumatic carditis requires careful auscultation because murmurs can be subtle during the first episode of RF. Subcutaneous nodules are relatively uncommon and seldom clinically obvious. They need to be searched carefully at specific locations. Erythema marginatum is uncommon, often very

Table 1 Differences between rheumatic heart valve disease in adults versus children

Features	Adults	Children
MV involvement	MS increasingly common as age advances	MR: most common
Mitral stenosis	Varying involvement of valve and the tensor apparatus; calcification seen in older patients	Juvenile form: severe involvement of tensor apparatus with subvalvular fusion
AV involvement	AR and stenosis	AS: distinctly uncommon
Atrial fibrillation	Common in adults with LAE	Uncommon
Left atrial and atrial appendage thrombus	Common especially in presence of atrial fibrillation	Uncommon
Manifestations of PVH	Typical clinical and radiologic features of PVH	Children adapt to high LA pressures through reactive pulmonary vasoconstriction. High LA pressures are better tolerated without substantial activity limitations. Lung signs (clinical examination or X-ray) typically underestimate the severity of PVH
PHT in relation to the severity of PVH	Proportionate increase	Disproportionate increase due to the presence of a significant reactive component

Abbreviations: MV, mitral valve; MS, mitral stenosis; MR, mitral regurgitation; AV, aortic valve; AS, aortic stenosis; AR, aortic regurgitation; LAE, left atrial enlargement; PHT, pulmonary hypertension; PVH, pulmonary venous hypertension; TV, tricuspid valve; PV, pulmonary valve; LA, left atrium.

Table 2 Pathology of rheumatic mitral valve disease and echocardiographic correlates

Mitral valve structures	Pathology	Echocardiographic correlates
AML	Thickening with restriction of mobility of the leaflets especially at the edges resulting in the characteristic diastolic doming	Thickening (> 3–4 mm) identified on echocardiograms, diastolic doming is easily identified on 2-D echocardiography
PML	Fixed to a greater extent by the fibrotic and shortened tendinous chords	Readily identifiable PML with total immobility characteristic a feature of chronic RHD irrespective of whether the dominant lesion is MS or MR
MV commissures in MS	Symmetric fusion of commissures resembling fish mouth	<i>Commissural fusion:</i> Identified in the parasternal short axis view during 2-D echocardiography. Calculation of the stenotic valve area done in this view along the free and fused margins of the leaflets
Tensor apparatus in MS (chords, papillary muscles)	<ul style="list-style-type: none"> • <i>Chords:</i> Thickened and shortened; extensive fibrosis that involves the chords, papillary muscles and the adjacent leaflets responsible for residual MS after balloon dilation of the valve • Rupture of chords may occur during an episode of acute RF resulting in severe MR • Lengthening of the chords has also been described 	<ul style="list-style-type: none"> • <i>2-D/3-D echocardiography:</i> Tensor apparatus well visualized, fibrosis and shortening of the tensor apparatus, reduction in leaflet mobility • Rupture of chords can be identified by examining the free edge of the leaflets. Often the AML is involved

Abbreviations: AML, anterior mitral leaflet; MS, mitral stenosis; MR, mitral regurgitation; MV, mitral valve; PML, posterior mitral leaflet; 2-D, two dimensional; 3-D, three dimensional; RF, rheumatic fever.

transient and cannot be easily seen in dark-skinned individuals. Rheumatic chorea often occurs late after the inciting streptococcal sore throat and is sometimes quite subtle.

The symptoms and physical signs (**Table 3**) of established RHD are related to the severity of the valve affliction and the individual lesions.

Mitral Regurgitation

This is by far the most common lesion seen in RHD. Fatigue is the most common symptom of significant MR and results from the inability of the heart to increase cardiac output effectively to keep pace with the requirements of the body during activity. Palpitations are common in MR because of a volume-loaded hyperdynamic left ventricle and tachycardia. Dyspnea is uncommon unless the MR is severe, acute or the left ventricular myocardium is failing. With failing left ventricle, the left ventricular diastolic pressure increases, the left atrial and pulmonary venous pressure increase and pulmonary congestion appears. Pulmonary arterial hypertension (PAH) follows significant pulmonary venous hypertension (PVH). Some children with chronic severe MR can have disproportionately severe PAH as a result of an exaggerated

vasoconstriction of the pulmonary arterioles. Physical examination is discussed in **Table 3**.

Acute MR results in severe symptoms in the initial stages. This is the direct result of elevation in pulmonary venous mean pressure that results in pulmonary congestion. Over a period of time, the left atrium dilates and becomes more compliant. The LV dilates and accommodates the extra volume and the LV end diastolic pressure declines. A substantial reduction in dyspnea follows. This situation is seen quite frequently following an initial episode of RF with carditis and severe MR. Over a period of time, symptomatic improvement occurs without significant reduction in the degree of MR.

Mitral Stenosis

Rheumatic MS is less frequently seen in children when compared to MR. However, very early onset of MS (juvenile MS) has been described (sometimes as early as 6 years). Juvenile MS is a distinct entity largely confined to parts of the world where RHD is endemic with a very high prevalence. PVH and pulmonary congestion is a direct and predictable consequence of elevated mean left atrial pressure that results from mitral stenosis. Dyspnea

is therefore much commoner than in isolated MR. PAH occurs as a consequence of PVH. The severity of PAH can be variable depending on the degree of *adaptive* pulmonary vasoconstriction. It is not unusual to see children with severe (juvenile) MS with severe pulmonary venous and arterial hypertension who have no apparent discomfort at rest in spite of extremely high pulmonary arterial and left atrial pressures. The severity of symptoms in MS is also critically determined by the duration of diastolic filling period. With tachycardia, diastole shortens to a greater extent than systole. Children with MS are therefore exquisitely sensitive to tachycardia that results from exercise, anxiety and fever and can worsen rather suddenly in the face of these precipitating events. Physical examination is described in **Table 3**.

Combined Valve Lesions (Mitral Regurgitation with Mitral Stenosis)

Combined lesions are frequent in RHD. Typically, MS and MR occur simultaneously. The hemodynamic and clinical consequences are significant because the valve does not open completely in diastole and leaks in systole. Clinical features of both MS and MR can be readily identified in most situations. Multivalve disease involving combinations of MV, AV and TV is common. It is important to precisely quantify the severity of involvement of all the valves to enable correct management decisions. For example, balloon mitral valvotomy (BMV) is precluded in any child with MR that is more than mild and commissural in origin when it occurs with MS. Similarly, the decision on whether or not the aortic valve can be left alone in a patient undergoing mitral valve repair or replacement is dictated by the severity of associated AR.

Chest X-ray in Rheumatic Heart Disease

Cardiac chamber enlargement and changes in lung vasculature may have to be noted. Left atrial and atrial appendage enlargement

almost invariably accompanies significant MV disease. Right atrial enlargement is seen in the context of pulmonary hypertension (PHT) and TV disease. Left ventricular enlargement occurs in the presence of AR and MR. Lungs show varying degrees of pulmonary venous congestion depending on the severity and duration of PVH (**Fig. 1**).

ECG

The ECG (**Fig. 2**) is relatively less sensitive but nonetheless very useful. Left atrial enlargement (LAE) and right ventricular hypertrophy is seen in pure or dominant MS. Left ventricular enlargement with volume overload in the form of q waves in lateral chest leads is seen in MR. Atrial fibrillation as a late consequence of RHD and is unusual in children even in the presence of severe LAE.

Echocardiography

Readily identifiable ECHO specific features in RHD with excellent pathological correlates allow confirmation of RHD (**Table 2**). Simultaneous involvement of multiple valves supports the diagnosis of RHD. The association of MV with AV involvement is infrequent in other conditions. However, there are situations where echocardiographic diagnosis is not straightforward (**Table 4**). It helps to correlate the echocardiographic findings with the clinical context.

The severity of individual lesions can be defined with precision. Gradients across the affected valves can be determined (**Figs 3A to C**) and the severity of regurgitant lesions (**Fig. 4**) can be quantified. The hemodynamic consequences of various lesions can be studied. These include upstream and downstream chamber enlargement, PHT and ventricular function. Serial echocardiography is often used to guide decision regarding timing of surgery. Important complications such as infective endocarditis (IE) can also be readily recognized.

Table 3 Cardiovascular examination in rheumatic mitral valve disease

Physical finding	Mitral stenosis		
	Mild	Moderate	Severe
S ₁	Loud	Louder	Loud/soft in tight MS
S ₂	Normal	S ₂ normal, splitting P ₂ : loud	S ₂ splitting, closer P ₂ : loud
OS	Yes	Earlier occurrence	
A ₂ -OS interval	Wide	Shortens	Shortens further
Other sounds			Systolic ejection click due to PHT
Murmurs	MDM: Relatively soft and late-onset often heard with the bell of the stethoscope, lying down and partially turned to the left lateral position. Murmur may be unmasked by exercise	Prominent MDM with presystolic accentuation	Prominent MDM with presystolic accentuation* Other murmurs: Harsh, ejection systolic murmur, early diastolic murmur of PHT, TR—pansystolic murmur
MDM			
Mitral regurgitation			
Apex beat	Normal apex	Hyperdynamic apex	Cardiac enlargement, downward and outward displaced apex, hyperdynamic precordium
Heart sounds	Normal S ₂ , no S ₃	Widely split S ₂ , S ₃ may be present	Widely split S ₂ (early A ₂), P ₂ may be loud if PHT develops, S ₃
Murmurs	Blowing apical pansystolic, usually not accompanied by a thrill, no flow murmurs. S ₁ merges with the murmur but may be loud and distinct in the presence of accompanying MS	Prominent pansystolic murmur	Frequently a mid-diastolic flow murmur without presystolic accentuation (unless associated with MS)

*Rarely, severe MS may not be associated with an identifiable MDM (silent MS); usually this is accompanied by severe PHT and gross right ventricular enlargement. Abbreviations: OS, opening snap; PHT, pulmonary hypertension; MDM, mid-diastolic murmur; TR, tricuspid regurgitation; MS, mitral stenosis.

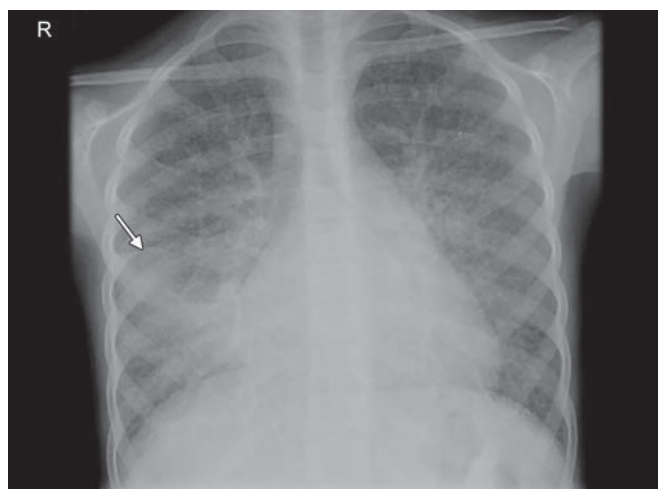


Figure 1 Chest X-ray (posterior-anterior view) from a child with juvenile mitral stenosis as a result of rheumatic heart disease. There is evidence of severe pulmonary venous hypertension in the form of prominent upper lobe pulmonary veins (cephalization), interstitial haze and prominent interlobar fissures (arrow). Additionally there is evidence of left atrial (lifting up of the left bronchus) and left atrial appendage (straightening of left heart border)

Echocardiographic Criteria for Established Rheumatic Heart Valve Disease

In some situations, especially when the lesions are mild, there is potential for incorrect labeling. A number of conditions need to be distinguished from rheumatic aortic and MV disease. It is also very important to have clear criteria when large population-based or school surveys of RHD are undertaken. The recently published World Heart Federation echocardiographic criteria allow uniform classification and categorization of RHD. This is particularly useful in clinically silent cases. This includes Doppler criteria and 2-D evidence of morphologic involvement.

SPECIFIC DIAGNOSTIC CHALLENGES

Recurrence of Rheumatic Fever

The challenge is to establish and diagnose active carditis in pre-existing RHD, because the other major criteria may not always be present in recurrent episodes. According to 2002–2003 WHO criteria, a diagnosis of recurrences of RF in the presence of RHD requires the presence at least two minor manifestations of RF plus evidence of preceding group A streptococcal infection [in the form of elevated antistreptolysin O (ASO) titers or a positive throat swab for group A β -hemolytic *Streptococcus*].

Infective Endocarditis

Infective endocarditis can complicate RHD induced regurgitant lesions of MV or AV. IE is rather uncommon in children with isolated MS. An incidence of 2.3% of IE was reported in a large study involving 1,763 RHD patients followed-up over an average period of 5.3 years. The consequences of infective endocarditis are often devastating. Any fever of more than 4–5 days in children with RHD warrants diagnostic work-up for presence of IE as early diagnosis with institution of appropriate antibiotic therapy is vital to limit or minimize further significant valve damage. Three or more blood cultures before administration of antibiotic are mandatory. Other indicators of endocarditis such as microscopic hematuria, leukocytosis, thrombocytopenia and elevations in acute-phase reactants have limited sensitivity and specificity. Echocardiography can identify vegetations on valves affected by RHD. Transesophageal ECHO improves sensitivity substantially, especially in older children.

OUTCOME: LONG-TERM COMPLICATIONS AND NATURAL HISTORY

Severe rheumatic MV disease results in heart failure that is the most common reason for premature death and disability. The key contributors to occurrence of heart failure are PHT, ventricular dysfunction, functional or organic TV involvement, endocarditis and dysrhythmias.

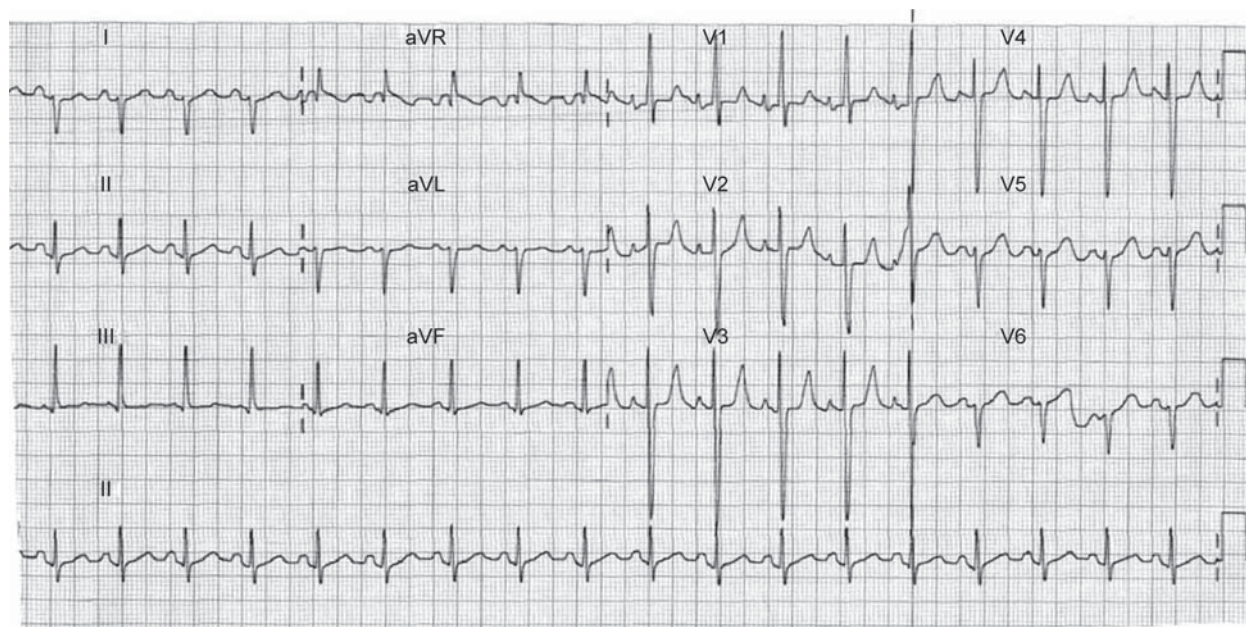


Figure 2 Electrocardiogram from a child with rheumatic heart disease and severe mitral stenosis. There is evidence of right ventricular hypertrophy in the form of rightward deviation of the QRS axis, prominent 'r' waves in V1 and persistent 's' waves in V5 and V6. Additionally there is evidence of left atrial enlargement in the form of prominent broad 'p' waves in lead II

Table 4 Differential diagnosis of rheumatic mitral valve disease from other abnormalities of mitral valve (by age of presentation and ECHO findings)

Condition	Specific differentiating features
Myxomatous mitral valve, MVP	<i>Leaflet mobility:</i> Never restricted; excessive mobility of parts of AML and PML with typically lengthened chordae, MVP typically seen in late systole, associated features include aortic root dilatation. ECHO distinction of chordal rupture in MVP may be challenging from that of acute RF
Isolated cleft in the MV	<i>AML:</i> Usually involved and readily identified by ECHO
Funnel-shaped MV	Fused chordae tendineae with normal papillary muscle arrangement may be confused with Rh.MS, earlier age of onset below 4 years of age unlike that of Rh.MS seen above 6 years of age
MV arcade	Abnormal tensor apparatus near insertion of the papillary muscles onto the valve with resultant severe MR at a very young age
Parachute MV	Readily identifiable single papillary muscle in parasternal short axis view, frequent obstructive lesions at other sites in the left heart (as parts of the Shone complex)
Double orifice MV	Valve tissue between anterior and posterior leaflets
Supramitral membrane	Readily identifiable by ECHO, characteristic origin of the turbulence across the MV at the level of the MV annulus
Inborn errors of metabolic infiltrative diseases of the connective tissue like Hurler's MPS	Early age of onset, dysmorphic features, hepatosplenomegaly, other systemic manifestations
Other inflammatory conditions	Typical absence of fibrotic changes in the MV tensor apparatus characteristically seen in RHD and preservation of leaflet mobility
Anomalous origin of left coronary artery from pulmonary artery (ALCAPA)	Early presentation in infancy, late presentation is rare, specific ECG changes, <i>ECHO:</i> MR may rarely be noted with scarred papillary muscle and relatively preserved LV function; Identifiable origin of the abnormal coronary artery with flow reversal in the left coronary artery

Abbreviations: MVP, mitral valve prolapse; MV, mitral valve; RF, rheumatic fever; MPS, mucopolysaccharidosis; AML, anterior mitral leaflet; PML, posterior mitral leaflet; MR, mitral regurgitation; RHD, rheumatic heart disease; LV, left ventricle.

Pulmonary Hypertension

Pulmonary hypertension frequently complicates RHD. It invariably accompanies severe MS and is frequently associated with severe MR in children. Overall PHT is most common in children in comparison to adults. The reasons for PHT include passive transmission of left atrial and PVH, interstitial edema and reactive pulmonary arteriolar vasoconstriction. PHT is a significant prognostic variable in RHD. It contributes substantially to right heart failure in children with RHD.

Resolution of the PHT has been studied following balloon mitral valvotomy. A part of the PHT that is attributable to passive transmission of elevated pulmonary venous pressure resolves immediately. The reactive component that contributes to elevated pulmonary vascular resistance resolves slowly over weeks to months.

Ventricular Dysfunction

Left ventricular dysfunction is usually the consequence of long-standing and severe MR or AR. The combined presence of severe MR and AR accelerates left ventricular enlargement and dysfunction and contributes to poor long-term outcomes following double valve replacement in children with RHD. Much of the damage appears to result from chronic volume overload; the weight of available evidence does not support a substantial role for myocardial injury during episodes of rheumatic carditis. The natural history of severe MR or AR is not well-characterized in children and this may be somewhat different from adults. Right ventricular dysfunction is a consequence of severe and long-standing PHT.

Infective Endocarditis

Infective endocarditis typically complicates MR or AR and is seldom associated with isolated MS. Endocarditis needs to be suspected in the face of persistent fever or sudden worsening of heart failure.

Dysrhythmias

Unlike in adults, atrial fibrillation is distinctly uncommon in children with RHD even in the face of severe LAE. Atrial fibrillation

has an important influence on the natural history of RHD. Uncontrolled ventricular responses typically herald the onset of atrial fibrillation. The resultant tachycardia often results in marked worsening of symptoms in patients with MS.

Thromboembolism

Severe atrial dilation results in stasis of blood in the left atrium (often visible as spontaneous contrast in echocardiograms) that promotes clot formation. The left atrial appendage (LAA) is the most frequent site for clots to form. Atrial fibrillation greatly increases the propensity for thrombosis. Clots may remain silent and organize in the LAA. However, there is a risk of dislodgement if BMV is attempted in the presence of a clot in the LAA. It is therefore vital to carefully interrogate the LAA through transthoracic and, if needed, transesophageal echocardiography before BMV is contemplated.

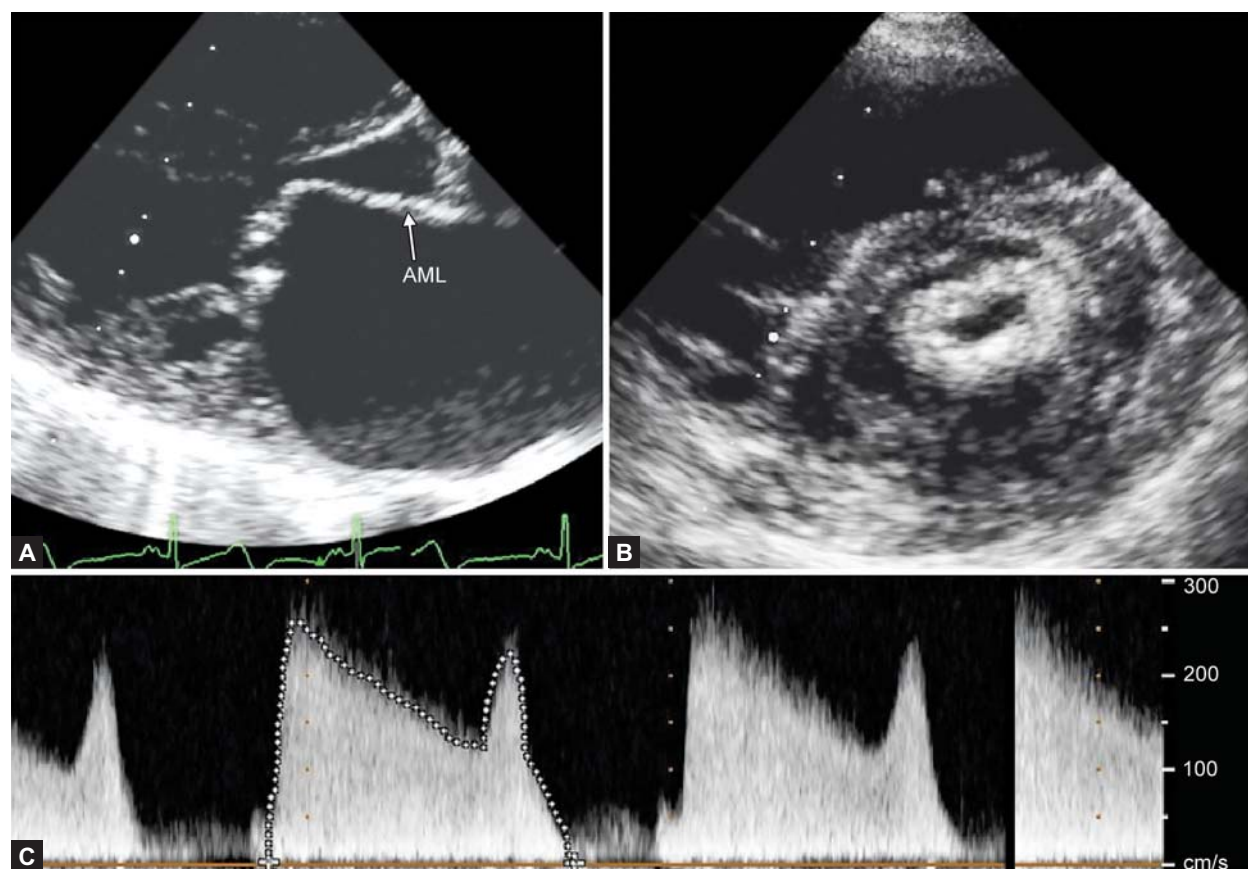
Recurrence of Rheumatic Fever

Patients with established RHD are at a particularly high risk of recurrence of RF following an episode of streptococcal sore throat. Recurrences of RF are almost invariably associated with carditis in these patients. Many episodes of RF recurrences are not clinically obvious and this is reflected in the relatively liberal WHO criteria for diagnosis of RF in the presence of RHD.

TREATMENT OF ESTABLISHED RHEUMATIC HEART VALVE DISEASE

Secondary Prophylaxis to Prevent Rheumatic Fever Recurrences

All patients with established RHD must receive secondary prophylaxis. This involves regular administration of penicillin to patients with established RHD, or one or more previous episodes of RF. The success with secondary prophylaxis is critically dependent on patient's education. Drugs, doses and duration of prophylaxis have been discussed in the previous chapter.



Figures 3A to C Two-dimensional echocardiography for rheumatic heart disease and mitral stenosis. The top panel shows a diastolic frame from the parasternal long axis view (A). The characteristic “dog-leg” or “elbow” deformity is shown in the anterior mitral valve leaflet (AML). The tips of the AML are thickened. The thick and shortened chordae attached to the posterior mitral leaflet are also shown in this frame. Frame B is a picture obtained from the parasternal short-axis view. This view captures the mitral valve orifice in mid-diastole and allows accurate estimation of the mitral valve area. This view is also very useful in planning balloon mitral valvotomy (BMV). In this patient, for instance, it can be anticipated that the commissures would split favorably after BMV. The lower panel (C) is a Doppler tracing from the same patient showing the characteristic ‘M’ shaped flow acceleration across the stenotic valve that is seen in patient with MS and sinus rhythm. The second peak results from atrial contraction and is responsible for the presystolic accentuation of the mid-diastolic murmur

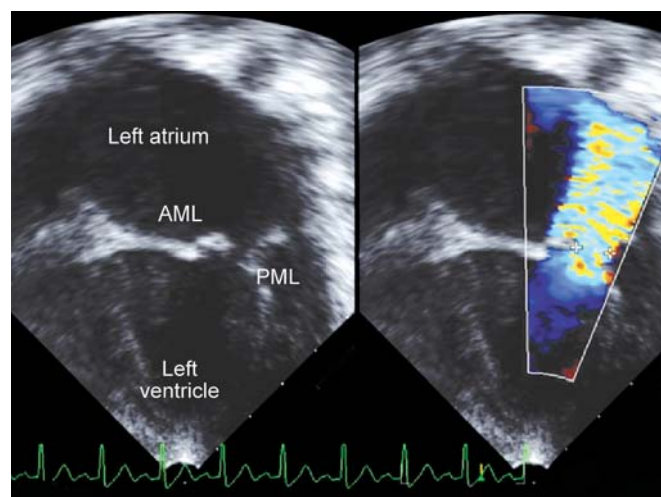


Figure 4 Echocardiographic images of severe mitral regurgitation in rheumatic heart disease. The anterior mitral leaflet (AML) is thickened. The tip of the AML is oriented horizontally and does not point downwards suggesting restriction of mobility of diastolic motion. The posterior mitral leaflet (PML) is also thickened and mobility is restricted to even a greater degree. The resultant color Doppler jet is directed posteriorly and laterally

Prophylaxis against Infective Endocarditis

Prophylaxis is no longer necessary unless there is likelihood of breach of oral mucosa, manipulation of either gingival tissue or the periapical region of teeth in presence of valve lesions that are at the highest risk of endocarditis. Thus, routine endocarditis prophylaxis is largely unnecessary for pure MV stenosis. High-risk lesions include the presence of prosthetic valve, AR and MR.

Drug Therapy for Heart Failure

Mitral Stenosis

Diuretics (typically furosemide) provide relief from symptoms of pulmonary congestion. Additionally, it often helps to reduce the heart rate both at rest and following exercise because heart rate reduction translates into an increase in diastolic filling period that helps reduce left atrial pressure. β -blockers have replaced digoxin because of a better efficacy and safety profile. β -blockers may prevent acute worsening of symptoms and occurrence of pulmonary edema and this has been documented in case reports. However, they do not appear to consistently improve exercise capacity in MS patients in sinus rhythm in systematic studies. β -blockers alone or along with a small dose of diuretic can be used in moderate MS and while awaiting BMV or in the event of suboptimal result following the procedure.

Regurgitant Lesions

Symptoms of pulmonary congestion accompanying severe MR or AR are treated mainly with diuretics. The role of systemic vasodilators to reduce systemic afterload in isolated MR and AR is controversial. The most commonly used vasodilators include angiotensin-converting-enzyme inhibitor (ACE) inhibitors and calcium channel blockers. Available data from adult populations do not support the role for administration of systemic afterload reducing agents to delay development of left ventricular dysfunction in MR. An important additional consideration in RHD is the presence of varying degrees of MS that accompanies MR.

In symptomatic patients with isolated severe AR, particularly in the presence of ventricular dysfunction, short-term therapy with vasodilators is perhaps indicated until AV surgery can be performed. In asymptomatic children with severe AR, there is really no evidence that the use of vasodilators have any role in delaying surgery.

Catheter Based Management of Mitral Stenosis

Balloon Mitral Valvotomy

Balloon mitral valvotomy also known as percutaneous trans-septal mitral commissurotomy (PTMC) is now a well-accepted minimally invasive interventional procedure for management of rheumatic MS in children. Improvement in MV area following BMV or PTMC is largely because of splitting of the fused commissures. The contribution of the subvalvar pathology to MS remains after BMV. As a result, MV area does not normalize after BMV.

The most popular dilatation of stenosed MV by BMV employs the Inoue balloon. The key initial step involves puncture of the interatrial septum with the Brockenbrough needle. The immediate results of BMV in children are comparable to adults. In a large series of 81 patients with juvenile MS, Bahl et al. demonstrated an increase in valve area by $172 \pm 62\%$ (from a mean of $0.8 \pm 0.4 \text{ cm}^2$ to $2.2 \pm 0.5 \text{ cm}^2$). The potential risk of BMV is occurrence of MR. With careful case selection, severe MR is rare.

Valve pathology is an important determinant of immediate and long-term outcome. Echocardiography allows assessment of a number of variables that can help predict the results of BMV both in terms of improvement in valve area and reduction in gradients and occurrence of significant MR. These variables include nature of commissural fusion, severity of subvalvar deformity, leaflet mobility and calcification. Trivial MR via the central valve orifice does not progress or may even disappear following BMV. However, MR at the commissures may progress following BMV.

Long-term follow-up after BMV is mandatory as there is a significant risk of restenosis with time. Restenosis is typically associated with significant residual MS (typically because of subvalvar pathology) following BMV. Repeat BMV is an option for restenosis and helps postpone open MV surgery.

Surgery

- **Rheumatic MS** Closed or open mitral commissurotomy is an effective surgical procedure that has been replaced by BMV.
- **Rheumatic MR** Repair of the MV should be considered whenever feasible as it is reported to offer excellent immediate and acceptable intermediate term outcomes. However, the results of MV repair in RHD with MR are not as consistently reproducible as they are for MR associated with myxomatous disease.
- **MR with MS** It is particularly difficult to deal with.

Additionally, there are major long-term concerns with RHD. There is evidence that the inflammation in chronic RHD continues well beyond the initial episode of RF and this may result in continuing injury to the heart valve and tensor apparatus after *successful* repair. There are several other challenges. Repeated operations are unrealistic in most environments where RHD is prevalent because

of the expense involved with open heart surgery. It is, however, equally important to recognize the limitations of MV replacement with a mechanical prosthetic valve in younger patients.

Monitoring anticoagulation is particularly challenging in most parts of the developing world. Pregnancy imposes a substantial additional risk in females. The surgical approach to RHD with MR needs to be individualized based on the valve pathology, gender, age, resources, surgical expertise, patient and family preference.

There are no clear guidelines for the timing of MV surgery (particularly replacement) in children. Persistent symptoms in spite of maximally tolerated medications warrant consideration of surgery especially in the face of pulmonary artery hypertension. For asymptomatic patients, any evidence of ventricular dysfunction clearly merits consideration for surgery. Standard guidelines for MV surgery in adults do not apply to children. The natural history of chronic valve regurgitation appears to be quite different in children when compared to adults. There is an urgent need to perform good prospective studies to study the natural history of MR in children.

For patients with RHD with combined mitral and AV disease, the threshold for replacing both valves is quite high in most environments. This is because of expense and morbidity and concerns regarding long-term outcome in the face of erratic anticoagulation. Many surgeons, therefore, choose to replace the valve that is severely affected (typically the mitral valve) and leave the less severely affected valve alone (often the aortic valve). It has been shown that the mild or moderate AV disease does not progress rapidly over several years after MV replacement for RHD.

Associated TV disease can be repaired in most instances. In almost all cases the mitral, aortic or both are affected. Typically, annuloplasty of the dilated TV annulus is sufficient to restore competence.

IN A NUTSHELL

1. MV is the most common valve involved in RHD in children with MR being the commonest lesion. Early-onset MS is largely limited to regions with high RHD prevalence.
2. A variety of conditions need to be considered in the differential diagnosis. Most common conditions include MV prolapse in association with myxomatous degeneration and congenital MV disease.
3. Advanced untreated RHD with MV disease is associated with premature death and morbidity from a variety of complications that include heart failure and endocarditis.
4. Medical management includes secondary penicillin prophylaxis and diuretics. β -blockers are useful in MS and vasodilators may be considered for MR.
5. Surgical management involves MV repair and replacement. Repair should be considered in isolated MR but requires an experienced and committed surgeon.
6. BMV is a useful option for isolated MS providing relief for many years.

MORE ON THIS TOPIC

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Chapter 40.31

Rheumatic Aortic Valve Disease

Savitri Shrivastava

Aortic valve involvement in rheumatic fever with carditis is not uncommon in developing nations. The aortic valve may be involved in the acute phase of illness, i.e., active carditis or later in the form of chronic valvar heart disease. Rheumatic carditis results in annular nodular thickening resulting in lack of coaptation and prolapse of the aortic valve, retraction of the aortic valve and annular dilatation.

In patients of acute rheumatic fever, the most common valvar lesion is mitral regurgitation which may be associated with aortic regurgitation (AR). Presentation with significant AR in acute phase of rheumatic fever is very rare. With first attack of rheumatic carditis, mild to moderate degree of echocardiographically demonstrated AR is reported to occur between 5% and 25% of children, but isolated AR is seen in less than 2–8% of cases. However, AR with mitral valve disease is much more common. The AR murmur is classically an early diastolic high-pitched decrescendo murmur after the second component of second heart sound. The management in the acute phase is like management of active rheumatic carditis, as discussed earlier.

AORTIC REGURGITATION

Aortic valve involvement in rheumatic heart disease (RHD) results in AR. Rheumatic aortic stenosis (AS) has never been described in literature in pediatric age group. Rheumatic involvement of the aortic valve results in distortion and retraction of the aortic cusps, which leads to noncoaptation of the cusps resulting in AR, the mitral valve is histologically always involved in the rheumatic process. Clinically, isolated AR, without associated clinical mitral valve disease, is rare and occurs in only 2–8% of patients with rheumatic fever and RHD, but AR with mitral valve disease either regurgitation or stenosis is much more common, seen in approximately 40% of cases.

HEMODYNAMICS

Aortic regurgitation is a backward leak from the aorta into the left ventricle (LV) during diastole. This increases the volume of blood reaching the LV which increases in size to accommodate the extra regurgitant volume from aortic run off. The LV size is thus directly related to the degree of aortic leak unless there is myocardial dysfunction. This increased LV volume results in palpitation, because of the backward flow of blood the forward flow is compensated by peripheral vasodilatation as well as increased ejection from the LV during early part of the systole. However, significant AR results in low forward output during exercise. The pulse pressure is wide because of increased systolic and lowered diastolic pressure. Signs of wide pulse pressure in the form of exaggerated arterial and arteriolar pulsations are invariably present except in mild AR or AR in failure. Slowing of heart rate increases the diastolic period and increases the regurgitant volume of blood in AR. With good left ventricular myocardial function even moderate AR is tolerated well for long periods, one-fourth of the patients of isolated AR can develop significant left ventricular dysfunction in later stages with the onset of left ventricular decompensation. With the failing myocardium, the left ventricular diastolic pressure rises and results in an increase in left atrial pressure and pulmonary venous hypertension which results in exertional dyspnea and audible third heart sound (S_3) and rarely fourth heart sound (S_4)

In later stages, the pulmonary arterial pressure may also rise resulting in loud pulmonary component of the second heart sound (S_2).

Significant LV dilatation is accompanied with abnormal stress on the mitral valve-papillary muscle complex. This may result in inadequate apposition of the mitral leaflets and appearance of mitral regurgitation.

CLINICAL FEATURES

Aortic regurgitation of mild to moderate degree is often well tolerated. The forward flow can be raised effectively on exercise. So, fatigue is not an early symptom. The large stroke volume and forceful left ventricular contractions results in palpitations which is the earliest symptom in patient of AR. Peripheral vasodilatation results in excessive sweating and heat intolerance. In severe AR with failing LV, dyspnea on effort occurs which can progress to orthopnea and to overt signs of pulmonary edema if not appropriately treated. Signs of AR are as follows:

- The pulse pressure is wide. The wider the pulse pressure, the more severe is the aortic leak.
- Prominent carotid pulsations (*Corrigan's sign*), visible arterial pulsations over the extremity vessels (*dancing peripheral arteries*) and visible pulsations of the abdominal aorta can be seen. These are signs of wide pulse pressure and can be seen in all other conditions which results in aortic run off.
- On holding the middle of the forearm or leg and elevating it a sharply rising and abruptly falling pulse wave can be felt. (*Corrigan's pulse* or *water-hammer pulse*).
- Nodding of the head may be present with each systole (*de Musset's sign*) due to sudden filling of the carotid vessels in severe AR.
- Arteriolar pulsations may be seen over the nail bed, uvula, lips, earlobes and in the eyes.
- *Hill's sign*: There is exaggeration of the systolic pressure difference between the brachial and femoral arteries. Normally, the difference between the systolic pressure in the brachial artery and the femoral artery is less than 20 mm Hg, the femoral systolic pressure being higher. Systolic pressure difference between 20 mm Hg and 40 mm Hg suggests mild AR. If the difference is between 40 mm Hg and 60 mm Hg, it suggests moderate AR. A difference of more than 60 mm Hg indicates severe AR.
- *Pistol shot sounds*: If the stethoscope is put over the brachial or the femoral artery without applying any pressure *pistol shot sounds* may be heard in moderate and severe AR.
- *Duroziez's sign*: A systolic murmur may be heard if pressure is applied to partially occlude the artery proximal to the chest piece of the stethoscope and a diastolic murmur will be heard if pressure is applied distally. This combination of systolic and diastolic murmurs is called *Duroziez's sign*.
- *Cardiac examination*:
 - Cardiomegaly is present with significant AR. The apex is displaced downward and outward, the degree of cardiac enlargement depends upon the severity of AR. The apex beat is ill-sustained LV type typical for left ventricular volume overload.
 - With severe AR, the whole chest wall may show a to and fro movement. Uncommonly, a diastolic thrill may be palpable at the upper left or right sternal border.
 - The first sound (S_1) is soft and the aortic component of the S_2 may be audible or may be masked by the regurgitant diastolic murmur. The split of the S_2 is normal with mild to moderate AR and with severe AR it may be single on paradoxically split particularly if left ventricular failure has set in.

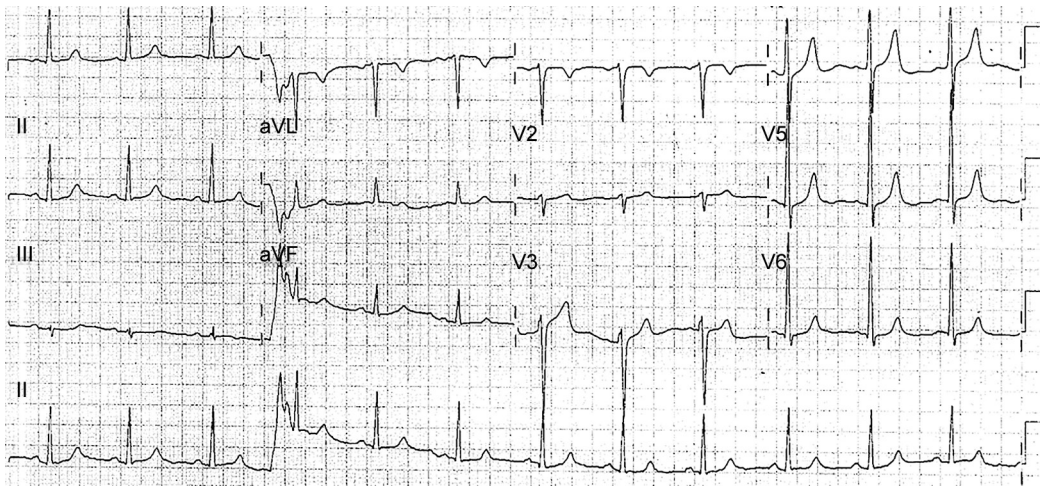


Figure 1 Electrocardiogram showing high voltages on left ventricular leads and tall T waves in a patient with significant aortic regurgitation

- The AR murmur is a high pitched blowing, decrescendo diastolic murmur starting with the aortic component of the S_2 . The length of the diastolic murmur depends on AR severity. With severe AR, it is pandsystolic. The murmur is best heard along the left sternal border mostly but may be heard at right sternal boarder. It radiates to the apex and even beyond the apex. The murmur is best heard with the diaphragm of stethoscope, withheld expiration and patient in leaning forward position.
- With large aortic leaks, there is also an ejection systolic murmur at the second right intercostal space conducted to the neck and not infrequently associated with a systolic thrill. The systolic murmur is the result of a large stroke volume passing across rough valve. It does not indicate AS if the pulse pressure is wide and the carotid upstroke is brisk.
- S_3 may be audible with significant AR and in patients with congestive heart failure. Rarely, if the left ventricular end diastolic pressure is severely elevated a left ventricular S_4 may be heard.
- Delayed diastolic rumbling murmur may be heard in late phase of diastole at the apex named Austin Flint murmur. The backward jet of AR hits the anterior mitral leaflet (AML) and mitral inflow, setting the AML in a flutter, well appreciated in M-mode echocardiography. Sometimes, this murmur may be confused with mitral stenosis murmur but loud S_1 , opening snap and presystolic accentuation of the mitral diastolic murmur is hallmark of mitral stenosis in patients with isolated AR.
- Signs of congestive heart failure are apparent in patients with failing left ventricle.

ELECTROCARDIOGRAM (FIG. 1)

Electrocardiogram (ECG) may be normal with mild AR, but with significant AR there will be signs of left ventricular volume overload. There are deep Q waves with increased left ventricular voltage in left sided chest leads accompanied with tall T waves. The pattern of deep Q waves and tall T waves has been called the diastolic overloading pattern of the LV. With onset on left ventricular failure, ST and T changes over left ventricular leads develop.

CHEST ROENTGENOGRAM (FIG. 2)

Cardiac enlargement of the left ventricular type with dilated aorta is seen in significant AR. There may be evidence of pulmonary



Figure 2 Chest X-ray showing cardiomegaly left ventricular type and prominent aorta in a patient with moderate aortic regurgitation

venous and arterial hypertension with severe AR and myocardial dysfunction.

TWO-DIMENSIONAL ECHOCARDIOGRAPHY WITH COLOR FLOW MAPPING (FIGS 3 TO 5)

Echocardiogram (ECHO) is an extremely useful modality in evaluating AR in children with RF and RHD. The 2-D profilation clearly shows the morphology of the aortic valve which helps in the diagnosis and also assessment of the reparability of the valve. The aortic root dimension and left ventricular size can be measured. If the left ventricular size is greater than or equal to 25 mm/m^2 or if there is progressive increase in left ventricular size, the surgical option has to be considered. The left ventricular diastolic as well as systolic function can be assessed. At the earliest indication of functional impairment surgery is the treatment of choice. On color flow mapping, the quantum of AR can be estimated by size of color flow regurgitation jet and the area occupied by the regurgitant blood in relation to the left ventricular cavity.

DIFFERENTIAL DIAGNOSIS

- *Conditions associated with a wide pulse pressure:* Patent ductus arteriosus, ventricular septal defect with AR, ruptured sinus

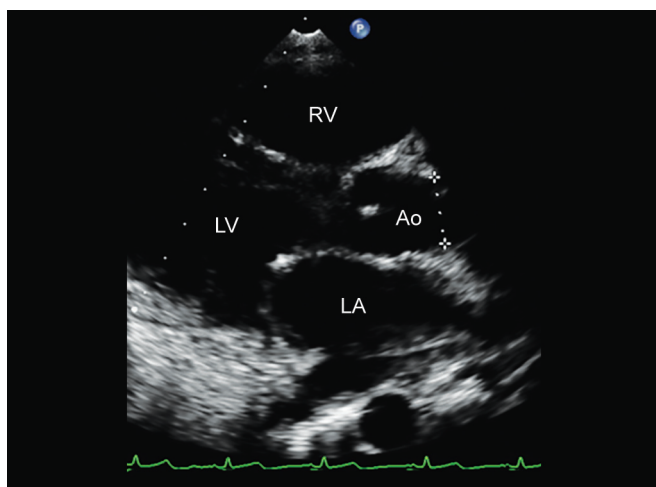


Figure 3 2-D echocardiogram (long axis view) showing dilated left ventricle (LV) and aorta (AO)

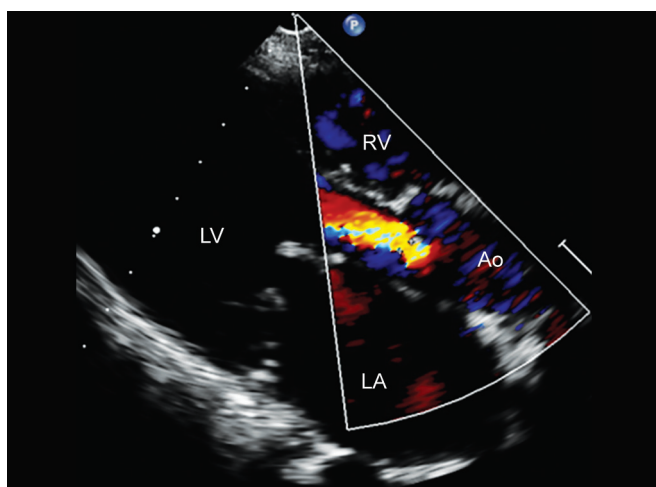


Figure 5 2-D echocardiogram with color flow mapping (long axis view) showing turbulent jet of moderate aortic regurgitation
Abbreviations: LV, left ventricle; Ao, aorta; RA, right atrium; LA, left atrium.

of Valsalva, arteriovenous fistulae—coronary or peripheral, anemia and thyrotoxicosis.

- *Conditions associated with a nonrheumatic AR:* Prolapse of aortic sinus with ventricular septal defect and AR, congenital aortic valve disease, Marfan syndrome, Hurler syndrome and idiopathic obstructive aortoarteritis.
- Conditions associated with basal early diastolic murmur of pulmonary regurgitation.

MANAGEMENT

Mild to moderate AR is known to be well tolerated for years with proper RF prophylaxis. Digitalis, though conventionally used to treat congestive cardiac failure (CHF) in RHD children; however, it is known to increase the regurgitant volume of blood by slowing the heart rate. Vasodilators, especially angiotensin-converting enzyme inhibitors are helpful as first line in severe CHF to tide over the acute condition before operation and should be the mainstay of management. If there is pulmonary venous hypertension and right-sided failure, diuretics and salt restriction should also be advised. Penicillin prophylaxis should be continued.

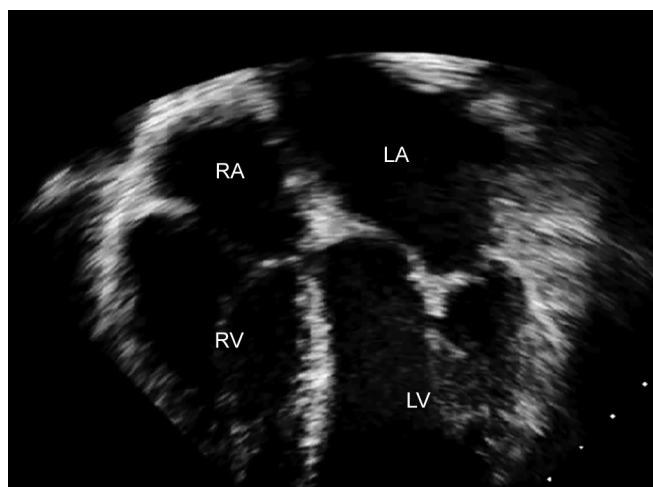


Figure 4 2-D echocardiogram (apical four-chamber view) showing enlarged left ventricle (LV), right atrium (RA), left atrium (LA) and right ventricle (RV)

In patients with significant AR with left ventricular end-diastolic dimension of greater than or equal to 25 mm/m², the patient will need aortic valve replacement. Aortic valve repair is mostly not possible as the aortic leaflets are markedly deformed. Ross procedure in which autograft, i.e., pulmonary valve of the patient is implanted in aortic position and homograft or a valved conduit is placed in pulmonary position can be performed. But Ross procedure has not shown promise in rheumatic AR. The only option left is prosthetic aortic valve replacement. The long-term results are good. The only problem is that lifelong anticoagulation and surveillance is needed. Timely surgery prevents development of ventricular dysfunction, pulmonary hypertension and arrhythmias.

Before a pediatric patient is sent up for valve replacement surgery, one should consider and treat effectively before undertaking re-evaluation of cardiac function and surgery: (a) presence of rheumatic activity since active carditis by itself can cause cardiac enlargement and (b) any anemia contributing to cardiac enlargement and symptoms.

IN A NUTSHELL

1. Aortic valve involvement in RHD results in AR.
2. Rheumatic AS has never been described in literature in pediatric age group.
3. Rheumatic involvement of the aortic valve results in distortion and retraction of the aortic cusps which leads to noncoaptation of the cusps resulting in AR; the mitral valve is histologically always involved in the rheumatic process.
4. Clinically isolated AR—without associated clinical mitral valve disease—is rare and occurs in only 2–8% of patients with rheumatic fever and RHD, but AR with mitral valve disease either regurgitation or stenosis is much more common, seen in approximately 40% of cases.
5. Palpitation is the earliest symptom in patient of AR. Examination reveals signs of peripheral runoff including a wide pulse pressure.
6. The AR murmur is a high pitched blowing, decrescendo diastolic murmur starting with the aortic component of the S₂.
7. Vasodilators, especially angiotensin-converting enzyme inhibitors are helpful as first-line drugs for treating heart failure in AR.

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Chapter 40.32

Takayasu Arteritis

Biswajit Bandyopadhyay

Takayasu arteritis is a chronic inflammatory disease of the aorta and its major branches. The disorder is a large vessel vasculitis (often granulomatous) of unknown origin that has been reported in pediatric patients as young as age 6 months and in adults of every age. In children, Takayasu arteritis is one of the more common etiologies of renovascular hypertension. Despite the term pulseless disease, which is a synonym for Takayasu arteritis, the predominant finding in individuals with Takayasu arteritis is asymmetrical pulse. Absent peripheral pulses occur late in the course of the disease. Although 5-year survival rates exceed 90%, the disease has a high incidence of residual morbidity.

ETIOLOGY

Takayasu arteritis is common in developing countries, where the disease is closely associated with tuberculosis. The nature of this association is unclear because most patients with Takayasu arteritis in the United States do not have tuberculosis. Spirochetes, streptococcal organisms and circulating antibodies due to an autoimmune process are also implicated. In endemic areas, active tuberculosis may perpetuate Takayasu disease activity through molecular mimicry or chronic antigen stimulation. Girls are twice as commonly affected as boys. Genetic factors may play a role in the pathogenesis.

PATHOPHYSIOLOGY

The clinical course of Takayasu arteritis is characterized by two often overlapping phases: (i) the acute, active inflammatory prepulseless phase and (ii) the chronic pulseless end-stage phase. During the acute, active prepulseless phase, histologic study demonstrates a granulomatous arteritis involving all layers of the artery, particularly the media. Characteristic changes of the pulseless end-stage phase of the disease include progressive intimal and adventitial fibrosis and extensive scarring and degeneration of the media changes associated with progressive segmental arterial stenosis, occlusion, dilation and aneurysm formation. Stenoses are the most common lesion, found in 90% of patients with Takayasu arteritis. Patients often have poststenotic dilatations and other aneurysmal areas, reported up to 45%. Endothelial activation leads to a hypercoagulable state predisposing the patient to thrombosis. Congestive heart failure in individuals with Takayasu arteritis may occur as a result of hypertension, aortic root dilation or myocarditis.

Human studies suggesting endothelial cell activation have demonstrated increased expression of intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) in patients with Takayasu arteritis. Evidence for an autoimmune etiology is supported by circulating antiaortic antibodies and antiendothelial cell antibodies found in the sera of patients with Takayasu arteritis. Immunoglobulin G (IgG), IgM and properdin deposits are found in lesions from pathologic specimens. Autoreactive T-cells, Th1 and Th17, are increased in active Takayasu arteritis along with decreased numbers of FOXP3-positive Treg cells.

Cytokine abnormalities include elevated tumor necrosis factor and interleukin (IL)-6. More recently, B-cells are identified as contributing to Takayasu arteritis with plasmablast expansion

in patients with active Takayasu arteritis. This increase in B-cells is not seen in inactive disease. IL-6 and B-cell activating factor (BAFF) also increase total numbers of circulating B-cells; reduction in disease activity is observed with successful depletion of B-cells with anti-CD20 and increase in B-cells observed with relapse.

CLINICAL FEATURES

Prepulseless Phase

Manifestations during the active inflammatory *prepulseless phase* include constitutional symptoms, intermittent nausea and vomiting, abdominal pain, arthralgia/arthritis, myalgia, cough, hemoptysis, pleuritis, transient skin nodules, transient episcleritis, headache, neurologic deficits, lymphadenopathy, anemia and elevated sedimentation rate. The peripheral pulses and blood pressures may be normal, making diagnosis difficult. Aortography may only demonstrate nonspecific thickening of the vessel wall.

Pulseless Phase

As the disease progresses into the chronic pulseless phase, additional symptoms and signs that make the diagnosis more obvious include extremity claudication, particularly in the arm; bruits over the cervical, supraclavicular and abdominal regions; absent or decreased brachial and radial pulses; a systolic blood pressure difference greater than 10 mm Hg between arms; decreased femoral pulses; aortic incompetence; hypertension; congestive heart failure; angina (from rare coronary artery involvement); hemiplegia; seizures; syncopal episodes and fundoscopic abnormalities, including the wreathlike anastomosis surrounding the optic disc, as originally described by Takayasu.

DIAGNOSIS

Acute phase reactants are elevated with leukocytosis and thrombocytosis. Erythrocyte sedimentation rate (ESR), transaminases and von Willebrand factor-related antigen are elevated. Antiendothelial antibodies are present. Antinuclear antibody results are usually negative. Rheumatoid factor is elevated in 15%. The biomarker pentraxin 3, a protein closely related to C-reactive protein, may be positive in some patients with active disease with a normal C-reactive protein. Matrix metalloproteinase (MMP)-9 is also synthesized and is elevated in active disease.

Determining Disease Activity

It is a major challenge because of poor correlation among clinical, laboratory, radiologic and histologic data. 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) has been evaluated in the assessment of disease activity; preliminary results were encouraging, showing high sensitivity and specificity for the presence of inflammation. However, the clinical usefulness of this test remains uncertain and its correlation with disease activity has been questioned.

Imaging Studies

During the chronic pulseless phase, chest radiography may show cardiomegaly, decreased pulmonary vascular markings, irregular contour of the descending aorta, dilation of the aortic arch and linear calcification of the aortic wall. Duplex color flow Doppler ultrasonography may reveal mural thickening and turbulent flow in the carotid arteries and abdominal aorta, stenosis and poststenotic dilation in the abdominal aorta, stenosis or occlusion of subclavian arteries and distal dampened

monophasic flow in the brachial arteries. Echocardiography can detect aortic root dilation, coronary artery involvement and the aortic and mitral valve regurgitation associated with Takayasu arteritis. MRI may reveal narrowing and occlusion of large arteries. Conventional thoracic and abdominal aortography provides the most complete and accurate assessment of the aorta and its major branches. Angiographic findings include stenosis (**Fig. 1**), occlusion, dilation and aneurysm formation in the aorta, its major branches and the pulmonary artery, and demonstration of collateral circulation. In children, the most commonly involved arteries in descending order are the abdominal aorta and renal arteries, thoracic aorta, subclavian artery, carotid artery and pulmonary artery. Less commonly involved are the superior mesenteric, celiac, vertebral, hepatic and coronary arteries.

TREATMENT

Pharmacological Management

During the active inflammatory prepulseless phase of the disease, the patient should be treated with prednisone, 1–2 mg/kg/day for approximately 1 month, followed by slow tapering over several months. However, although 60% of patients respond to this treatment, 40% relapse on steroid taper. Patients not responding to corticosteroids or who relapse during corticosteroid taper require an additional agent. Symptoms of patients who relapse on corticosteroid taper may be controlled with weekly infusions of methylprednisolone (30 mg/kg, not to exceed 1 g/week). However, extensive use of these infusions is associated with significant steroid-induced toxicity if continued for any significant period. Methotrexate, infliximab, etanercept, cyclosporine, cyclophosphamide and mycophenolate mofetil also allow disease control and weaning from steroids.

The presence of antiendothelial antibodies and plasmablast expansion in patients with active Takayasu arteritis suggest a role for B-cell based therapies. Reports using rituximab, monoclonal anti-CD20 antibody and tocilizumab (monoclonal anti-IL-6-receptor antibody) have described remission induction in Takayasu arteritis resistant to other treatments. Anecdotal reports of matrix metalloproteinase inhibition using minocycline suggest that this may be a useful adjunctive therapy which may also allow lower doses of corticosteroids, and thus reduced toxicity.

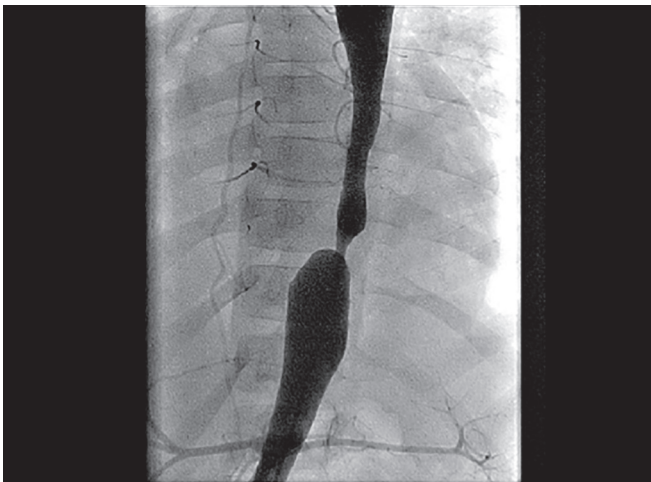


Figure 1 Nonsurgical interventions

Surgical Management

Whenever feasible, anatomic correction of clinically significant lesions should be considered, especially in the setting of renal artery stenosis and hypertension. Severe or progressive changes may require aortic surgery with or without valve replacement. Because of the high prevalence of subclavian and carotid stenoses in Takayasu arteritis, severe symptomatic stenoses of these vessels should be treated by grafts that originate from the aortic root and not from an arch vessel to another arch vessel. The latter may be followed by loss of the graft because of new stenosis in an initially spared subclavian or carotid artery. Conversely, a graft from the ascending aorta is a safer long-term conduit because the ascending aorta in Takayasu arteritis essentially never becomes stenotic. Mesenteric and celiac artery stenoses are usually asymptomatic and only rarely require surgery. Angioplasty and intravascular stents have met with restenosis far more often than bypass, which is preferred whenever feasible.

It is always best to operate on patients who are in remission; however, judgment of disease activity in Takayasu arteritis may be difficult. Consequently, all bypass surgeries should include vascular biopsy specimens for histopathologic evaluation. Findings from surgical specimens may help guide the need for postoperative immunosuppressive treatment.

Nonsurgical Interventions

Takayasu's arteritis is a chronic granulomatous arteritis that affects the large vessels with predilection to aorta and its branches. Chronic inflammation leads to stenosis of the involved vessels and rarely aneurysms. With the advent of percutaneous transluminal angioplasty (PTA), most of the large vessel stenosis can be treated without surgical intervention with or without stent placement. The uses include PTA with stenting of renal arteries thus treating the hypertension due to renal artery stenosis; the cerebral arteries thus preventing a cerebrovascular event; celiac and mesenteric arteries thus preventing mesenteric ischemia, subclavian and iliac arteries thus preventing limb claudication.

PROGNOSIS

More than half of patients with Takayasu arteritis achieve control on corticosteroids alone; however, their relapse rate is high and they require long periods of steroid treatment. Morbidities are related to ischemia and hypertension and include congestive heart failure, transient ischemic attacks, stroke and visual disturbances. Chronic, low-grade dissection of the aorta may cause recurrent chest pain for years. Upon autopsy, children with Takayasu arteritis who have died from acute rupture of the aorta have often been found to have evidence of multiple small dissections that did not progress. Survival rate at 15 years is as high as 95%.

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IN A NUTSHELL

1. Takayasu arteritis is a chronic inflammatory disease of the aorta and its major branches. The disorder is a large vessel vasculitis (often granulomatous) of unknown origin that has been reported in pediatric patients as young as age 6 months and in adults of every age.
2. Tuberculosis is the most common etiology in Indian settings.
3. In children, Takayasu arteritis is one of the more common etiologies of renovascular hypertension.
4. Despite the term pulseless disease, which is a synonym for Takayasu arteritis, the predominant finding in individuals with Takayasu arteritis is asymmetrical pulse. Absent peripheral pulses occur late in the course of the disease.
5. Although 5-year survival rates exceed 90%, the disease has a high incidence of residual morbidity.

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Chapter 40.33

Congestive Heart Failure

Parvathi U Iyer, Harsheen Kaur, Neeraj Awasthy

In the current era, heart failure (HF) has attained epidemic proportions in adults. So, there has been tremendous strides in the understanding of the pathophysiology and management strategies of HF in adults. Recently in 2013, the American College of Cardiology Foundation (ACCF) and American Heart Association (AHA) issued the *ACCF/AHA Guideline for the Management of Heart Failure: Executive Summary* which provides excellent clinical practice guidelines for the management of acute and chronic heart failure in adults. Unfortunately, such clear cut clinical practice guidelines are not available for pediatrics population.

Heart failure in infants and children is becoming an increasingly important cause of hospital admissions globally. The last two decades have witnessed huge advances in the field of pediatric cardiology and cardiac surgery with recourse to aggressive cardiac catheter interventions and complex cardiac surgery in infants and small children. These advances have led to increasing survival of complex and palliated cardiac disease and have generated a large and ever increasing pool of children and adolescents with HF. Pediatric HF thus poses an ever increasing economic, social and psychological burden on parents and the extended family due to the current trend of greater recourse to cardiac catheter interventions and palliative cardiac surgeries. So, though the prevalence of pediatric HF is less as compared to adults the overall impact of pediatric HF is still considerable and is expected to increase with time.

DEFINITION

Heart failure is a clinical syndrome characterized by the inability of the heart to supply cardiac output to meet the metabolic demands of the body. In case of infants, this requirement includes appropriate *growth and development*. Congestive heart failure can be divided into a low cardiac output and a normal cardiac output state.

Low output state is defined as *the inability to supply sufficient cardiac output to keep up with metabolic demands of the body*.

Normal output state is defined as *an ability to supply sufficient cardiac output but with elevated ventricular filling pressures*.

A child is said to be in *cardiogenic shock* if tissue perfusion is compromised secondary to pump failure or due to the low cardiac output state.

CLASSIFICATION

The traditional New York Heart Association (NYHA) classification of HF is not applicable to infants and small children. The Ross classification of HF was developed for HF assessment in infants and the modified Ross classification incorporated relevant issues like feeding difficulty and growth failure into a severity index (**Table 1**). The more recently developed New York University Pediatric Heart Failure index uses physiologic parameters to generate a severity based weighted score ranging from 0 (no HF) to 30 (severe HF). None of these are perfect scoring systems and have not been validated adequately in large numbers of children with congenital heart disease.

ETIOLOGY

Heart failure in pediatric population is mostly due to untreated or treated congenital heart disease, acute myocarditis or various forms of cardiomyopathy. In our country, acute and chronic rheumatic

Table 1 Modified Ross heart failure classification for children

Class I	Asymptomatic
Class II	Mild tachypnea or diaphoresis with feeding in infants Dyspnea on exertion in older children
Class III	Marked tachypnea or diaphoresis with feeding in infants Marked dyspnea on exertion Prolonged feeding times with growth failure
Class IV	Symptoms such as tachypnea, retractions, grunting, or diaphoresis at rest

heart disease continues to be an important cause of childhood and adolescent HF. In some parts of India, severe anemia, malaria, malnutrition, vitamin deficiencies, hypocalcemia and vitamin D deficiency are important, often missed but easily treatable causes of infant and childhood HF. This is in contrast to adults in whom coronary artery disease, hypertension and sometimes rheumatic and congenital valvar heart disease are the main causes of HF. Today, surgically treated congenital heart disease (operated tetralogy of Fallot [TOF] who develop pulmonary regurgitation in later life, Fontan operation for tricuspid atresia and other single ventricle situations) have become increasingly important causes of HF in young adults.

Important triggering factors of HF especially in emerging economies like India include acute anemia, rheumatic activity, infective endocarditis, intercurrent infections, electrolyte imbalances (hypocalcemia) and fluid overload. Other triggers of acute HF are arrhythmias (tachycardiomyopathy or bradyarrhythmias) arising de novo or after surgery for congenital or acquired heart disease (in the early postoperative period or late onset arrhythmias).

The most common cause of HF in infancy is due to left ventricular volume loading and pulmonary overcirculation due to large left to right shunts—isolated ventricular septal defects or in combination with large atrial septal defects or patent ductus arteriosus (PDA). On the other hand the most frequent cause of HF in older children and adolescents is regurgitant lesions—mitral and or aortic regurgitation or pulmonary regurgitation in late postoperative TOF. Pressure overload due to obstructive lesions (e.g., aortic valvar stenosis) causes an increase in ventricular afterload which finally leads to increased wall stress and myocardial hypertrophy decreasing the left ventricle (LV)/right ventricle (RV) cavity size. The cardiac output decreases, causing myocardial ischemia. In the neonatal period, babies with obstructive lesions (critical aortic stenosis, coarctation of aorta, aortic arch interruption) may rapidly develop HF, deteriorate swiftly and present in circulatory collapse.

At any rate, it is of paramount importance to exclude *structural heart disease* in pediatric HF since the majority can be either corrected or palliated today. Once structural heart disease has been reasonably excluded the causes of HF include intrinsic myocardial disease—myocarditis, cardiomyopathy, toxic, metabolic or infiltrative myocardial conditions. Sepsis is increasingly recognized to directly impact myocardial pump function adversely and cause HF. **Table 2** enumerates usual causes of pediatric HF and **Table 3** describes the causes of HF in neonates.

PATHOPHYSIOLOGY


Heart failure occurs due to either intrinsic myocardial factors or extrinsic pericardial factors. Extrinsic factors act by impeding venous return to the heart leading to a low cardiac output state. Extrinsic causes include acute and chronic constrictive pericarditis pericardial effusions and sometimes large pleural collections or large pneumothorax.

Table 2 Causes of pediatric heart failure (HF)

A. Structural lesions	
I. Congenital defects	
1. Volume overload	
a. Left to right (L-R) shunts	
i. Ventricular septal defect	
ii. Patent ductus arteriosus	
iii. Multiple L-R shunts	
iv. Aortopulmonary window	
b. Atrioventricular or semilunar valve insufficiency	
i. Aortic regurgitation	
ii. Mitral regurgitation	
iii. Tricuspid regurgitation	
iv. Pulmonary regurgitation after repair of tetralogy of Fallot	
2. Pressure overload	
a. Left-sided obstruction	
i. Severe aortic stenosis	
ii. Aortic coarctation	
b. Right-sided obstruction	
i. Severe pulmonary stenosis	
3. Anomalous origin of left coronary artery from pulmonary artery (ALCAPA)	
4. Complex congenital heart disease	
a. Single ventricle	
i. Tricuspid atresia	
ii. Fontan failure	
iii. Hypoplastic left heart syndrome	
iv. Unbalanced atrioventricular septal defect	
b. Systemic right ventricle	
i. L-transposition (corrected transposition) of the great arteries	
ii. Late postatrial switch for d-transposition of great arteries, intact interventricular septum	
II. Acquired heart defects	
Rheumatic heart disease	
Endocarditis	
1. Volume overload	
a. Atrioventricular or semilunar valve insufficiency	
i. Aortic regurgitation	
ii. Mitral regurgitation	
iii. Tricuspid regurgitation	
2. Pressure overload	
a. Mitral stenosis	
B. Structurally normal heart	
I. Primary myocardial disease	
1. Acute myocarditis	
2. Primary cardiomyopathy	
i. Dilated	
ii. Hypertrophic	
iii. Restrictive	
II. Secondary (highly relevant in India)	
1. Anemia	
2. Sepsis	
3. Severe shock	
4. Metabolic: Hypocalcemia	
5. Severe malnutrition, vitamin deficiency	
6. Arrhythmias	
7. Burns	
8. Infectious	
9. Toxic (diphtheria)	
III. Miscellaneous (highly relevant today)	
After heart surgery: Postcardiopulmonary bypass ventricular dysfunction	

Heart failure (HF) due to intrinsic *myocardial pump failure* occurs due to ventricular systolic, diastolic dysfunction or abnormal ventriculoarterial coupling, i.e., an exaggerated, inappropriate or abnormal afterload on a normal myocardium. Congenital or acquired defects causing right or left ventricular volume loading

Table 3 Causes of neonatal heart failure (HF)

Neonatal cardiac failure → Untreated → Shock	
<ul style="list-style-type: none"> • Obstructive left-sided cardiac lesions <ul style="list-style-type: none"> – Aortic stenosis – Hypoplastic left heart syndrome – Coarctation of the aorta – Interrupted aortic arch • Late presentation of <i>duct dependent</i> defects 	

lead to ventricular dilatation which is finally associated with *systolic dysfunction* or impaired myocardial pumping. Similarly congenital or acquired defects causing right or left ventricular pressure overload lead to ventricular hypertrophy which is associated with *diastolic dysfunction*. Diastolic dysfunction often referred to as *restrictive physiology* is a situation where there is increased resistance to left or right ventricular filling due to *stiff or noncompliant* ventricles giving rise to symptoms of congestion. It is important to recognize scenarios of predominant diastolic dysfunction since inotropes may worsen diastolic dysfunction. Inotropes are far more effective in primarily systolic dysfunction. The normal neonate has a restrictive physiology and exemplifies left ventricular diastolic dysfunction. Examples of right ventricular diastolic dysfunction include unoperated and operated TOF. Restrictive forms of cardiomyopathy is also an example of diastolic dysfunction. Not infrequently systolic and diastolic dysfunction coexist and HF management can then be challenging.

Why does Myocardial Pump Failure Occur?

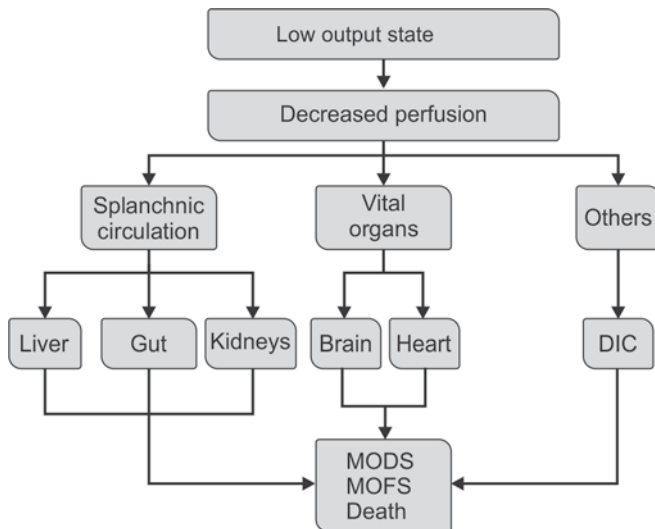
The cause of myocyte dysfunction is today thought to be multifactorial in etiology. There is increasing evidence that neurohumoral imbalance and an ionopathy with sodium and calcium dysregulation occur in HF. Reduced calcium has been shown to affect both systolic and diastolic performance. Inflammatory processes with increase in tumor necrosis factor α , interleukin-1 and actin disruption have all been shown to occur in pediatric HF. It is important to be aware of these advances since they have tremendous implications in current day management of HF.

Effect of Heart Failure

Heart failure if untreated goes on to develop diminishing cardiac output resulting finally in end-organ dysfunction, failure and death (**Flow chart 1**). In the presence of HF, i.e., whenever the heart cannot meet the requirements of the body at normal physiological filling pressures a number of *short-term adaptive* responses occur. These may be considered as a *hemodynamic defense response* aimed at improving myocardial systolic, diastolic function, overall myocardial performance and thereby increasing cardiac output. These responses occur through the release of a host of intrinsic humoral mediators which include epinephrine, norepinephrine, angiotensin II, aldosterone, arginine vasopressin and endothelin. These humoral mediators act by:

- Increasing the heart rate and blood pressure
- Increasing the contractility of the ventricles, and
- Augmenting the ventricular preload—all in an attempt to sustain normal cardiac output to meet the needs of the body (**Flow chart 2**).

Once these compensatory mechanisms fail, clinical features of HF evolve. Thereafter, a series of *maladaptive cardiac responses* due to prolonged pulmonary congestion and anasarca ensue leading to a process of *myocardial remodeling* with myocardial hypertrophy or

Flow chart 1 Effect of untreated heart failure—low cardiac output state

Abbreviations: DIC, disseminated intravascular coagulation; MODS, multiple organ dysfunction syndrome; MOFS, multiple organ failure syndrome.

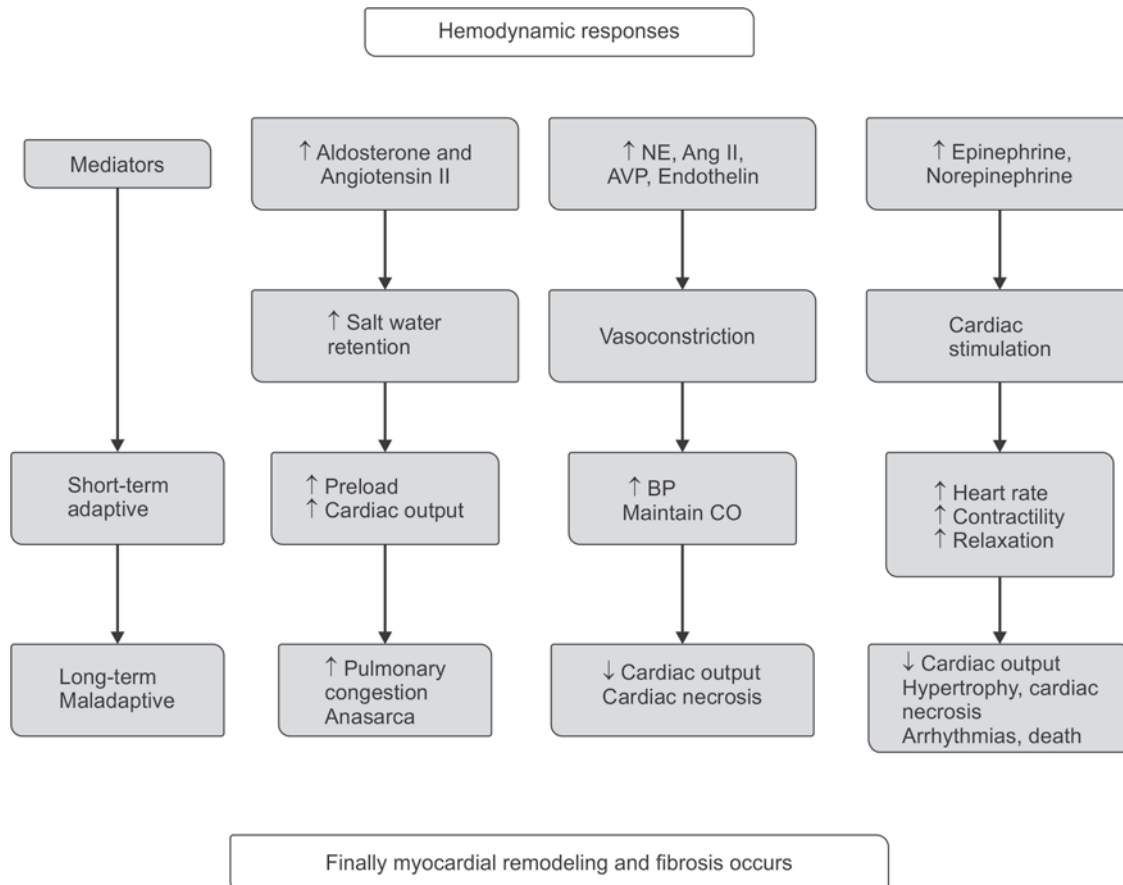
dilatation, fibrosis and gradually increasing myocardial apoptosis (programmed myocardial cell death). This myocardial remodeling leads ultimately to myocardial dysfunction and worsening or refractory heart failure with a tendency to malignant arrhythmias and finally death (**Flow chart 2**). These myocardial changes occur as

a result of—(1) upregulation of the renin-angiotensin-aldosterone system (RAS) causing greatly increased aldosterone levels and (2) sustained increasing levels of catecholamine (epinephrine, norepinephrine) and endothelin 1. A counter regulatory system evolves in the body with the release of cardiac hormones—atrial natriuretic peptide (ANP) and B type natriuretic peptide (BNP) in an attempt to neutralize the maladaptive neurohumoral responses. These hormones have the benefic effects of vasodilation and natriuresis. Thus, florid refractory HF can be interpreted as a major neurohumoral imbalance in the body with failure of the counter-regulatory system.

CLINICAL FEATURES (TABLE 4)

Once compensatory mechanisms fail, clinical features of HF develop. Left to right shunting or a protected pulmonary circulation in cyanotic heart disease, e.g., truncus arteriosus, double outlet RV cause pulmonary overcirculation and pulmonary congestion. Symptoms of HF in infants include resting tachypnea due to pulmonary congestion and secondary feeding difficulty leading to a suck-rest-suck cycle. There is often associated sweating or diaphoresis most prominent on the forehead. The feeding difficulty leads to failure to gain weight and finally weight loss. If florid HF develops then the infant may actually gain weight due to all the maladaptive responses (particularly upregulation of the RAS)—the increased aldosterone levels causing fluid retention and apparent weight gain.

Older children and young adults present typically with palpitations due to the compensatory tachycardia, and with worsening exercise tolerance progressing finally to breathlessness at rest and in the supine position.

Flow chart 2 Adaptive and maladaptive hemodynamic responses in heart failure

Abbreviations: Ang II, angiotensin II; NE, norepinephrine; AVP, arginine vasopressin; BP, blood pressure; CO, cardiac output.

Table 4 Symptoms and signs of heart failure (HF)

- Symptoms
 - Infants
 - Resting tachypnea
 - Feeding difficulty
 - Suck-rest-suck cycle
 - Diaphoresis
 - Failure to thrive
 - Older children
 - Palpitations
 - Exercise intolerance
- Signs
 - Chest retractions
 - Chest signs
 - Tachycardia
 - S₃ gallop
 - Puffiness around eyes
 - Hepatomegaly
 - Features of systemic congestion
 - Occasionally anasarca

Physical examination in infants reveals puffiness of the eyes, chest retractions exaggerated during feeding, along with chest signs—crepitations or crackles and hepatomegaly. In florid HF there may be anasarca along with desaturation in room air. Typically, pedal edema is not prominent in young infants. Cardiac evaluation classically shows tachycardia associated with an S₃ gallop. Chronic HF may also cause stunting with weight and height below the third centiles for age.

Patients with right heart dysfunction, such as pulmonary regurgitation in postoperative TOF or tricuspid regurgitation (rheumatic or Ebstein anomaly) predominantly have systemic venous congestion with prominent neck veins in older children and an increase in liver size.

INVESTIGATIONS

Exercise stress testing is only of relevance in older children and has little relevance in infants and small children. Biomarkers—B-natriuretic peptide and N-terminal pro-B-type natriuretic peptide are elevated in decompensated HF and have been used to titrate therapy in pediatric HF.

Chest X-ray

It reveals cardiomegaly and varying degrees of fluid in the lung parenchyma. There may be fissural fluid, small basal pleural effusions and occasionally florid pulmonary edema. Conditions with large left to right shunts or pulmonary overcirculation have increased pulmonary vascular markings or plethora. Sometimes the contour of the heart may provide a clue to the underlying structural heart defect, e.g., a hugely enlarged right atrium suggestive of tricuspid incompetence (**Figs 1 and 2**).

Electrocardiography

A normal electrocardiography (ECG) does not exclude HF. The most consistent finding is sinus tachycardia as a reflex response to HF. Other common findings are ST-T wave changes. ECG can validate findings of conduction delays and provide important clues to the causation of HF, e.g., left ventricular hypertrophy in LV pressure load conditions. It is important to note that ECG is not a sensitive indicator of ventricular volume loading.

Echocardiography

It is the single most important investigative tool in pediatric HF. A thorough study very effectively confirms or excludes structural

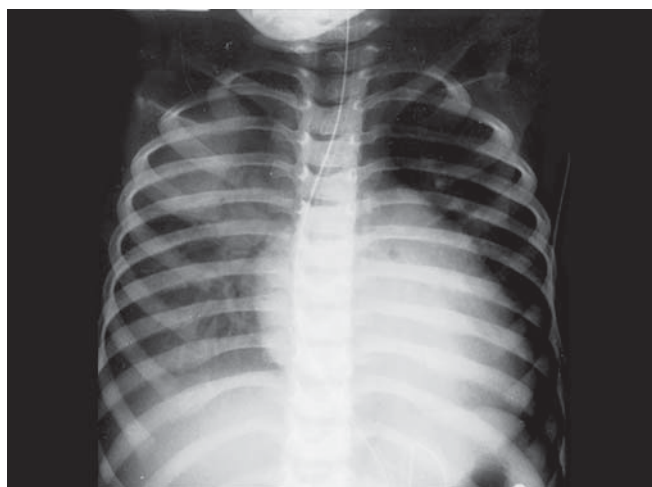


Figure 1 Hemorrhagic pulmonary edema in acute mitral regurgitation

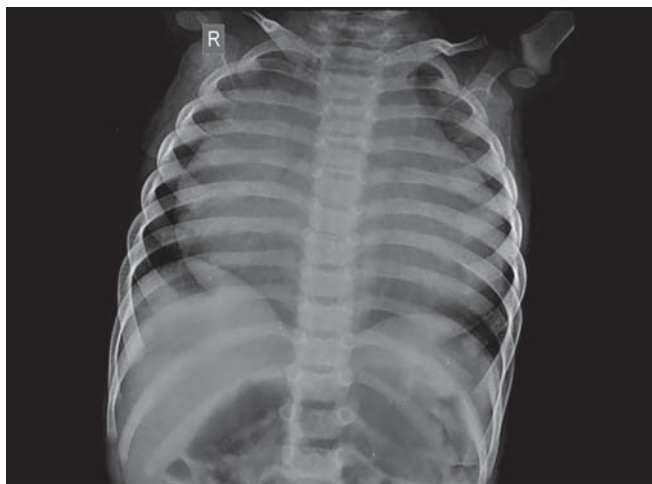


Figure 2 Enlarged right atrium in heart failure (HF) due to tricuspid regurgitation

heart disease after which HF management can be appropriately planned. Echocardiography (Echo) also provides useful information about ventricular volumes and ventricular systolic and diastolic function. Thus, serial echoes can be used to monitor ventricular dysfunction and fine-tune therapy of HF.

Newer Noninvasive Imaging Tools

Computed tomography (CT) angiography and cardiac magnetic resonance imaging (MRI) are only used to clearly define and elucidate various structural anomalies and confirm and clarify anomalies suspected on an echocardiogram. Today, cardiac MRI is also an invaluable tool to serially accurately monitor ventricle volumes for more precise timing of valve replacement in pulmonary regurgitant lesions. Thus, today many new exciting imaging modalities are available which help finetune decision making in pediatric HF.

TREATMENT

The goals of treatment are: (1) to minimize the mismatch between metabolic demand and supply (2) improve cardiac output (3) relieve symptoms of HF and (4) correct or palliate underlying structural defect. Thus, optimal management of HF involves much more than rational drug therapy.

Minimize the Mismatch between Metabolic Demand and Supply

All attempts must be made to minimize the mismatch between metabolic supply and demand. Factors that increase metabolic demands such as fever, anemia, intercurrent infections, chest infections, endocarditis, hyperthyroidism, rheumatic activity, tachyarrhythmias must be assiduously looked for and aggressively treated. Oxygen therapy and good airway management are useful in reducing the work of breathing and improving tissue oxygen delivery. Increasingly, noninvasive ventilation with nasal continued positive airway pressure (CPAP) or bilevel positive airway pressure (BIPAP) is being used both to reduce the work of breathing as well as to improve cardiac output in situations of increased ventricular filling pressures. Assisted ventilation may be needed to optimize cardiac output and tissue oxygen delivery in *acute decompensated HF* or pulmonary edema. Therapeutic hypothermia or targeted temperature maintenance at 35–36°C has been shown to be useful in reducing metabolic demands in acute severe decompensated HF or cardiogenic shock. Planned *nutritional therapy* (NT) with hypercaloric gavage feeds in infants with HF has been shown to both reduce metabolic demands as well as to improve weight gain and growth. Hypothyroidism must be looked for and treated as it compounds HF.

Improving Cardiac Output: Drug Therapy

Heart failure therapy in children includes management of chronic HF as well as management of acute decompensation. This is achieved by a number of drugs that improve cardiac output and relieve symptoms. These drugs involve standard therapy—preload reducing agents (diuretics), drugs that enhance myocardial contractility (digoxin), afterload reducing agents (angiotensin-converting-enzyme inhibitors [ACEi]) and some drugs more recently evaluated. Drug therapy recommendations in pediatric HF has largely evolved from adult data and from collated clinical experience in children. Pediatric data even for standard drug therapy is limited and comprises of small studies, or case series with very few randomized controlled trials (RCTs). The 17th Expert Committee on the Selection and Use of Essential Medicines List for Children (EMLc) reviewed digoxin, diuretics, aldosterone inhibitors, ACE inhibitors, beta-blockers, inotropes angiotensin receptor blockers (ARBs) and some newer drugs for HF.

Digitalis

It is a glycoside with the following characteristics—positive inotropic effect with improvement in baroreceptor function, increased vagal tone, decrease in circulating norepinephrine levels, and possibly aldosterone antagonistic effects (reducing renin

levels)—thus improving oxygen demand supply balance. However, only one adult study—DIG trial showed some treatment benefit in NYHA class II–III adults with reduced hospitalizations but no mortality benefit with digoxin. There was no treatment benefit with digoxin in the PROVED and RADIANCE trials—in adults NYHA class II. There are no RCTs available in children.

Thus, there is no robust evidence to support the use of digoxin—the traditional mainstay of therapy for HF. However, due to long established clinical practice the expert committee recommended that digoxin be retained in the list of drugs for HF therapy. Dosages, etc., are mentioned in **Table 5**. Drug interactions with carvedilol need to be remembered. So, currently, digoxin usage in HF is dependent on unit practices and preferences.

Diuretics

These have been considered to be a fundamental part of HF management particularly in volume loaded ventricles. The rationale for use has been the increased sodium and water loss induced by diuretics. Again no large RCTs are available in pediatric literature. Diuretics from different groups (a–c) can be combined for greater efficacy: (a) Loop diuretics, e.g., furosemide, torasemide, (b) Thiazides: Hydrochlorothiazide, metolazone (thiazide-related drug), and (c) Aldosterone antagonists, e.g., spironolactone and eplerenone.

Furosemide It continues to be the principle drug used in volume-overload conditions to decrease pulmonary congestion and thus decrease the work of breathing. The rationale for the use of furosemide is the increased water and salt loss through the kidney. Long-term use has been associated with sensorineural hearing loss in a small number of patients. However, currently it is the least toxic diuretic and one for which maximum experience is available. Torasemide is a loop diuretic more potent than furosemide, (10 mg of torasemide is equivalent to 40 mg of furosemide), has a higher bioavailability and a longer duration of action. In an open label study on children, torasemide was considered superior to furosemide for control of HF. However, it is currently not recommended for routine use.

A phenomenon associated with diuretic use is *braking* or refractory edema induced by increasing resistance to diuretic use with reducing urine output. Adult data has shown that combination therapy with thiazides or with metolazone increased sodium and water excretion with improved diuretic efficacy. A small pediatric study has also confirmed treatment benefit with combination of furosemide and metolazone.

No large RCTs on diuretics are available in children. The evidence for furosemide use is based on the adult Cochrane data base 2006: 14 studies with 514 participants (adults) showed

Table 5 Usual digitalizing and maintenance dosages for digoxin in children with normal renal function based on lean body weight

Age	IV digitalizing dose (µg/kg)	Daily IV maintenance dose (µg/kg)
Premature	15–25	20–30% of the IV digitalizing dose
Full term	20–30	25–35% of the IV digitalizing dose
1–24 months	30–50	
2–5 years	25–35	
5–10 years	15–30	
Over 10 years	8–12	

- Rapid digitalization is usually not indicated in heart failure (HF). Digoxin *holiday* is generally not needed in children. The half-life of digoxin is markedly prolonged in preterm babies and in renal dysfunction. Dose of digoxin should be halved when using amiodarone. IV digitalizing doses are 80% of oral digitalizing doses. Divided daily dosing is recommended for children under 10 years of age. Digitalizing dose: ½ dose stat and remaining dose in 6–8 hours interval depending upon clinical response.
- Digoxin has a narrow therapeutic range. Side effects include arrhythmias—sinus bradycardia, sinoatrial and atrioventricular blocks, atrial ectopics, atrial tachycardia with block, ventricular arrhythmias including ventricular tachycardia (VT); *gastrointestinal*—nausea, vomiting, abdominal pain and diarrhea; *central nervous system*—lethargy, confusion, disorientation, seizures; and ocular—blurred vision, diplopia, photophobia.

improvement in exercise capacity and reduced risk of both deterioration and death. A review of pediatric HF in 2004 concluded that furosemide should be part of the treatment pathway for HF in children. So, due to widespread availability and longstanding use, furosemide has been retained as the diuretic of choice in the list of essential drugs recommended by the expert committee (EMLc). While combination therapy with intermittent dosing of metolazone may be useful in *resistant edema* neither metolazone or other thiazides are currently included in the EMLc list due to lack of robust evidence.

Aldosterone antagonists (Spironolactone) The rationale for use are its multiple effects apart from reduced sodium and water retention. These drugs have the additional benefic effect of: (1) an improvement in tachycardia—improving oxygen demand-supply balance, (2) reduced myocardial apoptosis and fibrosis, and (3) antiarrhythmic effect. A landmark adult paper—randomized aldactone evaluation study (RALES) showed significant reduction in both mortality and symptoms. In pediatrics, there is very little robust evidence for treatment benefit but preliminary data indicates that spironolactone may reduce myocardial hypertrophy and fibrosis in chronic HF. If so, the incidence of malignant arrhythmias and sudden death may also diminish. So, though the evidence for spironolactone use in pediatrics is modest it is still included in the EMLc.

Thus, current recommendations are that in pediatric HF loop diuretics—furosemide be used as first-line drugs and many units worldwide would combine it with spironolactone for its potential multiple benefic effects.

Angiotensin-converting Enzyme Inhibitors (Captopril, Enalapril, Ramipril)

These drugs improve cardiac output by *afterload reduction*. ACE inhibitors antagonize the actions of angiotensin II. They decrease the effect that occurs from activation of the RAS system that occurs in HF. The beneficial effects of ACE inhibitors are: reduced angiotensin II mediated vasoconstriction, potentiation of sympathetic nervous system activity and reduced angiotensin II mediated aldosterone release. Thus, benefic effects include reduced sodium and water retention, reduced myocardial fibrosis and reduced inhibition of nitric oxide release along with reduced breakdown of vasodilatory bradykinin. Thus, the net effects are the reduction in systemic afterload along with symptomatic improvement.

Today, ACEi therapy is the mainstay of outpatient therapy for adults with HF. The evidence in children includes only one RCT which showed no benefit, the rest being case series. Majority of the case series showed some clinical benefit, some even showed survival benefit with some demonstrating improvement in LV function and hypertrophy. The adverse effects noted were hypotension, renal injury and occasionally death in very bad hemodynamic substrates. So, it is uncertain if the death could be directly attributed to the drugs. Another important side effect is a troublesome cough which is caused due to decreased breakdown of vasodilatory bradykinin. The cough resolves on cessation of the drugs.

A recent review in 2006 concluded that ACEi must be used in children with ventricular dysfunction and that use in valvar insufficiency is also appropriate and effective. Left to right shunts should be surgically treated and not managed with ACEi inhibitors. ACEi may be given only if surgery is not appropriate. The maximum pediatric data is on captopril and enalapril though enalapril has the advantage of less dosing requirements—once to twice/day. Captopril is given at least three times daily.

ACEi are not included in the EMLc but has been strongly recommended for inclusion in the list. Captopril has been proposed as most representative. Our practice is to use ACEi for ventricular dysfunction and occasionally for residual valve regurgitant lesions.

Angiotensin Receptor Blockers (Losartan, Candesartan)

The rational for use is that they reduce angiotensin II mediated vasoconstriction, potentiation of sympathetic activity and angiotensin II mediated aldosterone release. There is today increasing evidence that they offer therapeutic benefit in adults with HF. However, there is little data in children to support their use in HF and it is currently not recommended for use in pediatric HF and is not included in the EMLc.

Hydralazine

It is a peripheral vasodilator that is safe in patients with renal impairment as it does not produce much hyperkalemia. The starting dose is 0.75 mg/kg/day which may be increased gradually up to maximum of 5 mg/kg/day in four divided doses in patients who do not tolerate ACEi.

Beta-blockers (Carvedilol, Metoprolol)

Beta-blockers act by the following mechanisms—they cause slowing of heart rate—improving oxygen demand supply balance, reduce myocardial apoptosis and myocardial fibrosis. They also have anti-arrhythmic effect, vasodilatory and antioxidant properties and most important show synergism with ACE inhibitors. β -blockers were viewed previously with skepticism but currently they are the standard of care in adults with HF. Carvedilol, a third generation β -ARB is the most commonly used drug. Pediatric literature includes only retrospective small studies involving carvedilol, metoprolol. Some RCTs have also been done. One RCT showed no clear cut benefit. Majority of the studies show improvement in symptoms, systolic function, and synergism with other therapy. Higher doses are needed as compared to adults. β -blockers are not included in the EMLc list but there are strong recommendations to include carvedilol in addition to other conventional therapy. Current practice in many units including ours is to use carvedilol as adjunctive therapy for systolic ventricular dysfunction (cardiomyopathy, myocarditis and congenital heart disease).

Table 6 provides dosages of the drugs (other than digitalis) used to treat heart failure in children.

Management of Acute Decompensation

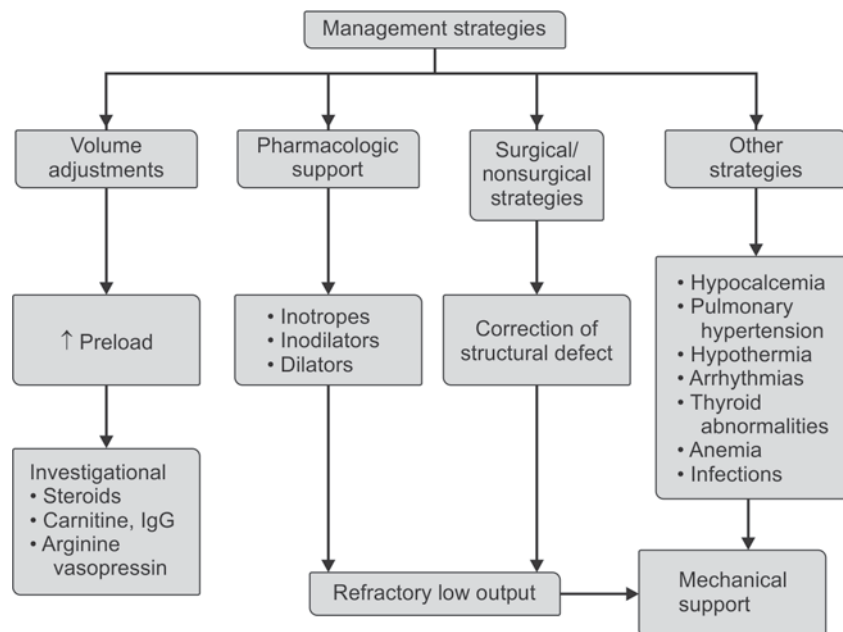
Many children present to the pediatric emergency room (ER) with acute decompensation in HR and its management remains a challenge. The investigative tools essentially remain the same as highlighted in the text earlier, that is to assess the degree and cause of decompensation and to investigate for any precipitating cause—*anemia, infections, endocarditis, etc.* A generalized management approach is highlighted in the **Flow chart 3**.

Gentle volume augmentation and judicious use of inotropic agents remains the initial approach for any child presenting with acute decompensation. Before the use of inotropic agents occult hypovolemia needs to be recognized and treated. The preload needs to be monitored by measuring the central venous pressure (CVP). Edema should be avoided and preload optimization needs to be done judiciously. The volume augmentation needs to be within the narrow range of the curve from B to C wherein there is no edema or pleural collection (**Fig. 3**).

Fluid overload in acute HF and pulmonary edema are best treated with intravenous furosemide—infusions combined with bolus dosing being most effective. In the absence of a satisfactory response to intravenous furosemide, furosemide infusion (0.2–1 mg/kg/hour) is often effective in initiating a brisk diuretic response and improving pulmonary congestion.

Table 6 Drugs for treating heart failure in children

Drug	Dosage	Side effects
<i>Furosemide (Lasix)</i>	<i>Neonate:</i> 0.5–1 mg/kg IV/IM q8–24 hour; maximum dose 2 mg/kg <i>Children:</i> 1–2 mg/kg PO/IV/IM; increase by 1–2 mg/kg, maximum dose: 6 mg/kg <i>Infusion dose:</i> 0.1 mg/kg/hour, can be doubled every 2 hours to maximum 1 mg/kg/hour	Hypokalemia, hyponatremia Metabolic acidosis, hyperuricemia Hyperglycemia Ototoxicity Nephrocalcinosis
<i>Spironolactone (Aldactone)</i>	<i>Neonate:</i> 1–3 mg/kg/day PO every 12–24 hours <i>Children:</i> 1.5–3.3 mg/kg/day PO in divided doses every 6–12 hours	Hyperkalemia (in renal failure) Gynecomastia Irregular menses, amenorrhea Gastritis, GI bleeding
<i>Metolazone</i>	0.1–0.2 mg/kg/day PO in single daily dose or divided q12 hourly	Severe hypokalemia Dry mouth, excessive thirst Weakness, drowsiness Light headed, restlessness Numbness, tingling sensation Palpitation, chest pain Decrease urine output
<i>Enalapril</i>	PO: 0.08 mg, maximum 0.5 mg/kg/day q12 hourly; not to exceed 5 mg/day	Hypotension (initial doses) Cough
<i>Captopril</i>	<i>Neonates:</i> 0.05–0.1 mg/kg dose q8–24 hour; maximum 0.5 mg/kg/dose <i>Infants:</i> 0.15–0.5 mg/kg/dose q8–24 hour; maximum 6 mg/kg/day <i>Children:</i> 0.3–1.0 mg/kg/dose q8–24 hour; maximum 6 mg/kg/day. Maximum 2 mg/kg/dose	First dose hypotension, cough Loss of taste sensation Insomnia Skin itching and rashes Drowsiness, headache
<i>Carvedilol</i>	Initial dose 0.05 mg/kg/dose twice daily. Increase every 2 weeks by 0.05 mg/kg/dose for the first increment then by 0.1 mg/kg/dose for the next increment, aiming for a maintenance dose of 0.35 mg/kg/dose given twice daily (not more than 25 mg twice daily)	Bronchoconstriction Bradycardia Heart block Hypotension Weight gain Giddiness

Flow chart 3 Management of acute decompensated heart failure**Inotropes, Inodilators****(Dopamine, Dobutamine, Milrinone)**

These drugs are used since they increase myocardial performance and cardiac output. Milrinone is an effective inodilator since it also decreases afterload. Indications for use include acute heart failure, cardiogenic shock and acute exacerbation of chronic heart failure (infections, anemia). Inotropy and lusitropy are synergistic

in improving cardiac output and dobutamine or dopamine may be judiciously combined with milrinone. Cardiogenic shock and acute deterioration are rarely sudden and typically result from gradual unrecognized deterioration. A meticulous and thorough echo examination is imperative to exclude structural, intrinsic and restrictive heart disease. It is also important to avoid a situation of increasing catecholamine dosing which would finally lead to catecholamine resistance (**Flow chart 4**). Alternative treatment

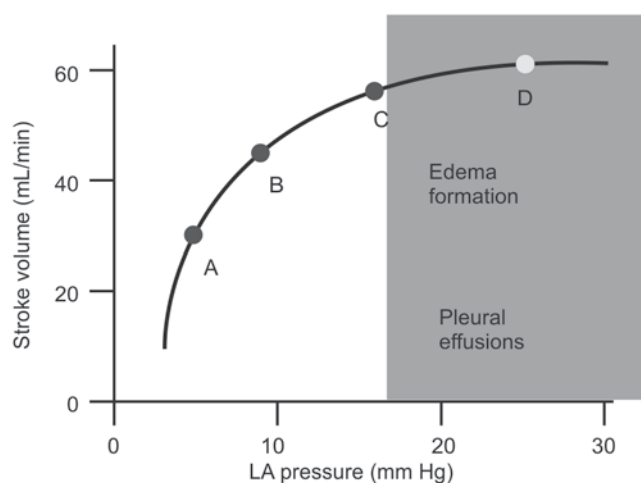


Figure 3 Preload and stroke volume/cardiac output

modalities other than high dose catecholamines need to be explored.

Hypocalcemia and Calcium Supplementation

Calcium is an essential part of the contraction and relaxation cycle of the myocardium and is often overlooked when HF is being treated. The neonatal and infant myocardium is particularly sensitive to extracellular calcium. It is the most common cause of systolic ventricular dysfunction in infancy in India. It is certainly the most easily correctable cause of ventricular dysfunction. Hypocalcemia is commonly seen in neonates, small infants especially if growth reduced or, malnourished or on diuretic therapy.

Indications for calcium supplementation are If ionic Ca less than 0.9 mmol/L, calcium infusion is required in the form of Ca gluconate 10%, 0.4 mL/kg/hour—titrated to ionic calcium levels—target levels being 1.2 mmol/L. Our protocol is to collect blood samples for vitamin D, parathyroid and alkaline phosphatase levels before initiating therapy for hypocalcemia.

Miscellaneous Modalities

Intravenous Immunoglobulins

Intravenous immunoglobulin (IVIg) is an immunomodulator, affecting B- and T-lymphocyte function and is known to neutralize

pathogenic antibodies and suppress their synthesis. IVIg is considered useful in the acute stage of viral replication and is part of the care pathway for acute viral myocarditis in infants who present with acute HF. Infants with elevated cardiac enzymes (Class IIa) or those with evidence of the acute nature of the illness on MRI are candidates for therapy.

Anticoagulant Drugs

Heart failure with severe ventricular dysfunction predisposes to clot formation, secondary strokes and pulmonary embolism. Those with gross HF and severe ventricular dysfunction should receive oral anticoagulants (Class I). Oral anticoagulants are also preferred for children with cardiomyopathy who have significant ventricular dysfunction (left ventricular ejection fraction [LVEF] < 20%) (Class IIa). The target international normalized ratio (INR) is kept between 2.0 and 3.0. If intracavitary thrombus or marked dilatation of atria with spontaneous contrast is present, anticoagulant therapy is again warranted (Class I).

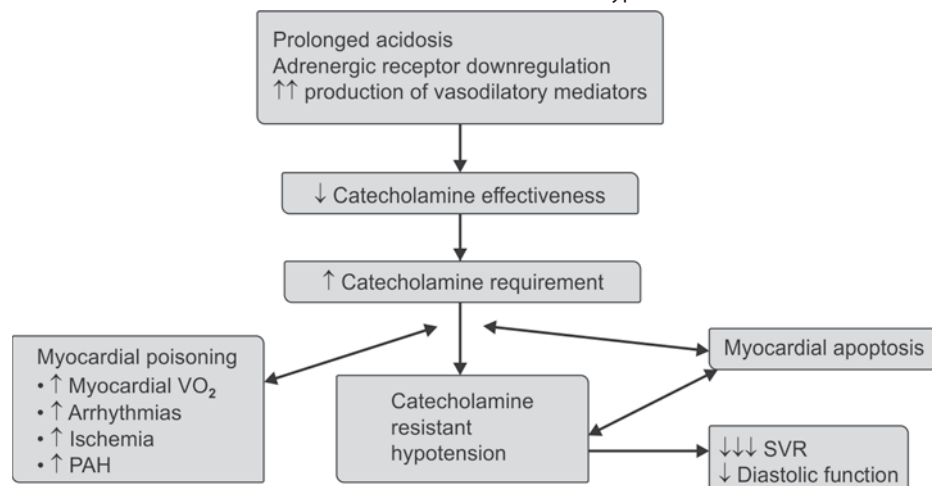
Catheter or Surgical Interventions

Structural heart disease with pressure overload conditions, e.g., aortic stenosis, coarctation of aorta, can cause severe acute left ventricular systolic dysfunction and acute HF with or without pulmonary edema. In severe cases, prostaglandin E1 infusion may be necessary to keep the ductus arteriosus open so that the systemic blood supply is maintained from the pulmonary artery via the PDA-aorta. Treatment of HF in this circumstance requires optimizing hemodynamics followed by urgent intervention—catheter intervention or balloon valvuloplasty for aortic valvar stenosis and emergency surgery for coarctation of aorta. Similarly, severe pulmonary valvar stenosis is managed by balloon valvuloplasty. Likewise, anomalous origin of left coronary artery from pulmonary artery may present with acute HF and severe left ventricular dysfunction on echo mimicking myocarditis to the unwary. Early surgical correction after initial stabilization is essential. Ventricular systolic function usually improves rapidly after catheter or surgical interventions with resolution of HF.

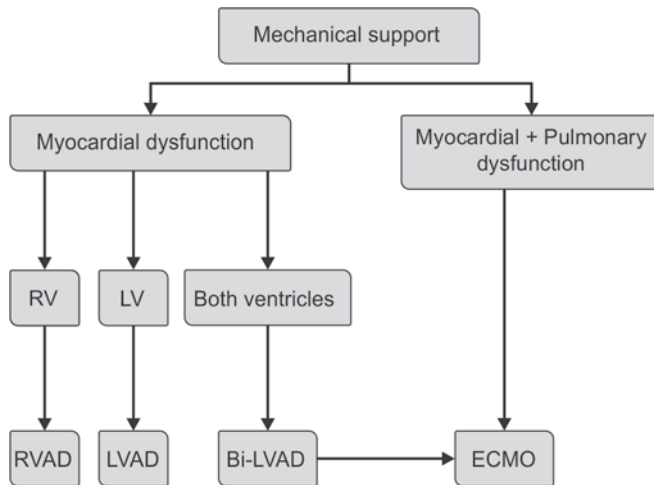
Mechanical Circulatory Support

The challenge in acute pediatric heart failure is that frequently infants and children present with severe left ventricular or biventricular dysfunction not readily responsive to drug therapy. These are typically children with severe myocarditis or end-stage cardiomyopathy. Mechanical circulatory support (MCS) management (**Flow chart 5**) is *acute* or *long-term*.

Flow chart 4 Catecholamine resistant hypotension



Abbreviations: PAH, pulmonary arterial hypertension; SVR, systemic vascular resistance.

Flow chart 5 Mechanical circulatory support (MCS)

Abbreviations: VAD, ventricular assist device; ECMO, extracorporeal membrane oxygenation.

Acute mechanical support or extracorporeal life support (ECLS) is of two types: (1) ventricular assist device (VAD) is a type of mechanical support that supports the ventricles and is less invasive; (2) extracorporeal membrane oxygenation (ECMO) is highly invasive and supports both the heart and the lungs. Both need prolonged anticoagulation, are highly labor intensive and highly expensive with an approximate discharge mortality of 50% (ELS organization registry). ECLS is also associated with significant side effects, e.g., bleeding, strokes, infection.

It must be remembered that ECLS is a bridge to recovery or to heart transplantation. The number of patients on the heart transplant recipient list is ever increasing worldwide and a decision to offer ECLS as *rescue therapy* should be carefully considered by the entire team. ECLS is not to be offered as destination therapy or as indefinite chronic therapy since it is not geared to provide long-term support.

Long-term mechanical support includes paracorporeal devices and implantable devices. Long-term MCS may be used as rescue therapy, temporary therapy, i.e., a bridge to transplantation or destination therapy, i.e., partial or complete myocardial recovery. These include—(1) pneumatic pulsatile pediatric ventricular assist devices (VADs)—The Berlin Heart EXCOR: These extracorporeal systems have provided successful MCS in children of all ages. They provide a long-term bridge to heart transplantation while allowing extubation, ambulation, and active physical therapy, unlike ECMO or centrifugal pump VADs. (2) The Micromed DeBakey VAD Child: This system has also been successfully used as a bridge to transplantation in cases which are NYHA Class IV end stage HF and are refractory to medical therapy.

Outpatient Treatment for Chronic Refractory Heart Failure

Inotropes, Inodilators (Dopamine, Dobutamine, Milrinone)

Inotropes have been traditionally used in acute HF for stabilization in severe acute cases, e.g., myocarditis. Also, they act as a bridge to cardiac intervention or surgery. In Chronic HF, they have been given in adults weekly on an outpatient or day admission basis. Short pulses of low-dose inotropes have been shown to reduce hospital admissions as well as provide symptomatic relief. They act as a bridge to recovery or transplantation. Some units have tried this strategy in children with chronic HF with varying success.

Newer Drugs in Severe Heart Failure

Nesiritide (synthetic brain natriuretic peptide) has been shown to increase diuresis in HF and improve renal failure with reduction in systemic venous congestion and considerable relief in symptoms.

Levosimendan is a calcium sensitizer and a potent inodilator agent. It offers *cardioprotection*—a new paradigm in the management of HF. It has also been used for *postoperative rescue* in severe infant low cardiac output state as well as in cardiogenic shock due to acute myocarditis after failure of conventional inotropy.

Surgical and Device Therapy

Pacemaker and Implantable Defibrillator

The indications for pacemaker in infants having HF are ventricular bradycardia or tachyarrhythmias. Implantable defibrillator is used in congenital heart disease patients who have syncope or tachycardia.

Cardiac resynchronization therapy (CRT) Dyssynchrony in myocardial contraction commonly occurs in patients with HF and left bundle branch block, leading to impaired LV function and worsening mitral regurgitation. CRT restores normal contraction to the LV wall while improving overall heart function. This should be considered after optimizing conventional drug therapy. Clear cut indications for CRT in adults are laid down. In pediatric patients CRT has been successfully tried in postoperative TOF patients with dyssynchrony. Its long-term benefit, though is yet to be established.

Continued Positive Airway Pressure

CPAP is an effective treatment for chronic HF. It has been shown to improve left ventricular dysfunction and cardiac output along with relief of symptoms. Domiciliary CPAP may be used in children with chronic HF due to cardiomyopathy or ventricular dysfunction due to myocarditis.

Other Surgical Strategies

Other surgical alternates for chronic decompensated HF include Batista operation or partial left ventriculectomy, myosplint device/Acorn cardiac device and passive restraint devices. All of these are intended to reshape the ventricle but are not associated with consistent success in controlling HF. *Heart transplant* has recently been performed in children.

Nutrition and Exercise in Heart Failure

Nutritional therapy with appropriate calories and proteins is of paramount importance in infants with congenital heart disease and has been discussed earlier in this chapter. Sodium restriction is not a requirement in children. Furthermore, limiting sodium can cause delayed body and cerebral growth. Normal physical activity should be continued in children with HF. Limiting exercise has not shown any favorable results. Published data has shown that cardiac rehabilitation programs led to sustained improvements in exercise function in children with HF. However, children with HF should not be permitted to participate in competitive sports.

Future Directions

Several new drugs are in various stages of clinical application. These include adenosine antagonists, nitric oxide modulators, natriuretic peptides, xanthine oxidase inhibitors.

Stem Cell Therapy

A promising modality represents the first realistic strategy for reversing the effects of what has until now been considered *terminal heart damage*. Many cell types have been successfully transplanted into damaged myocardium, including fetal cardiomyocytes, skeletal myoblasts, embryonic stem cells and bone marrow-

derived stem cells. The skeletal myoblast, an immature muscle cell that retains the ability to proliferate seems to be the most promising. It remains to be seen if engraftment of these cells leads to long-term improvements in LV function.

Gene Therapy

Gene transfer The three different biological pathways that play a crucial role in the pathophysiology of HF and form the target for gene therapy include intracellular calcium signaling, β_1 -adrenergic receptor (β_1 -AR) signaling, and antiapoptotic signaling. Intracoronary delivery of a recombinant adenovirus has been shown to improve global left ventricular function. Large clinical trials with long-term follow-up are needed before recommendations can be made.

IN A NUTSHELL

1. The prevalence of pediatric heart failure (HF) is less as compared to adults but the overall impact of pediatric HF is still considerable and is expected to increase with time.
2. Clinical assessment of severity of HF is important to titrate therapy.
3. Structural heart disease must be carefully looked for in pediatric HF. Once excluded it is important to assiduously search for various easily treatable metabolic and other causes of reversible HF.
4. Pathophysiology of myocardial failure is important to guide management. *Myocardial pump failure* occurs due to ventricular systolic, diastolic dysfunction or abnormal ventriculoarterial coupling, i.e., an exaggerated, inappropriate or abnormal afterload on a normal myocardium. The cause of myocyte dysfunction is today thought to be multifactorial in etiology. This multifactorial etiology has implications for therapy.
5. Heart failure (HF) can be interpreted as a major neurohumoral imbalance in the body with failure of the body's compensatory mechanisms.
6. Diagnosis of HF in pediatrics is largely clinical. The cause can be usually confirmed on echocardiography. Echocardiography also provides information on systolic and diastolic ventricular function as well as ventricle volumes. Thus serial echoes are useful in monitoring HF therapy. Serial biomarkers have also been shown to be useful in titrating and fine-tuning HF management. Cardiac MRI is more accurate than echo for ventricular volumes.
7. Provisional recommendations for drug therapy in HF constitute conventional modalities—digoxin, furosemide, spironolactone and inotropes in acute decompensated HF. There are strong recommendations to include ACE inhibitors (captopril/enalapril) and beta-blockers (carvedilol) as adjunctive therapy for HF management.

MORE ON THIS TOPIC

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Chapter 40.34

Infective Endocarditis

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Infective endocarditis (IE) is defined as an *endovascular microbial infection of cardiovascular structures*. It is a serious infection associated with significant morbidity and mortality and is becoming more frequently recognized in children and adolescents. Since the first description by William Osler in 1885, many advances have been made in its diagnosis and therapy. But due to the occult nature of this disease, the primary physician must have a high degree of suspicion to make an early diagnosis so as to institute prompt and appropriate antibiotic treatment for optimal outcome and prevent disease related complications.

EPIDEMIOLOGY

Incidence

Most children with IE have an identifiable risk factor for the disease. The incidence and epidemiology of IE has changed in recent times. The cumulative risk of IE up to 18 years of age was reported to be 6.1 per 1,000 children. Factors implicated for the increase in incidence of bacterial endocarditis are given in **Table 1**.

The median age of IE has however reduced from 8 years to 1.5 years. 42% of children with IE have an underlying congenital heart disease (CHD). In developing country like India, rheumatic heart disease continues to be an important cause of IE. Hospital-acquired IE is on the rise and causative pathogens are nonstreptococcal and nonstaphylococcal microbes.

Risk Factors

There are definitive risk factors identified for the occurrence of IE in children and adults (**Table 2**). A prior history of endocarditis is an important independent risk factor for subsequent IE; reported recurrence risk ranges from 2.5% to 9%. Patients with CHD in which blood is ejected at high velocity through a defect or a stenotic orifice are the most susceptible. The other CHDs predisposing to IE include left ventricular regurgitant lesions, coarctation of the aorta and tetralogy of Fallot. Vegetations usually form at the site of the endocardial or intimal erosion resulting from the turbulent flow.

Surgical correction of CHD may reduce, but does not eliminate the risk of endocarditis, with the exception of repair of a simple atrial septal defect or patent ductus arteriosus. Children who have undergone valve replacement or valved conduit repair are at particularly high-risk. As a corollary, cardiac lesions like secundum atrial septum, mitral valve prolapse with low velocity flows are at low-risk for IE.

Table 1 Factors implicated for the increase in incidence of bacterial endocarditis

1. Increase in postcardiac surgery survival for congenital heart diseases (CHDs)
2. Application of innovative cardiac surgical techniques
3. Use of prosthetic tubes and valves for surgery
4. Use of indwelling vascular catheters in infants admitted to intensive care units
5. Lack of awareness amongst the physicians, dentists, and general public, about the threat of IE and the preventive measures available

Table 2 Risk factors for bacterial endocarditis

Congenital heart diseases (CHD)	Bicuspid aortic valve Ventricular septal defect Patent ductus arteriosus Semilunar valvular stenosis Coarctation of the aorta Tetralogy of Fallot Left ventricular regurgitant lesions Cardiomyopathies
Acquired heart diseases	Rheumatic valvular heart diseases: Mitral regurgitation (MR), mitral stenosis (MS), combined MS and MR Aortic regurgitation and aortic stenosis Cardiomyopathies
	Postsurgical: Valve replacement with prosthesis, Conduit repair for CHDs Insertion of intracardiac devices (i.e., defibrillators or pacemakers)
Risk for right-sided IE	Indwelling catheters in intensive care units*

*Right-sided IE of the heart are associated with a very high mortality rate especially in neonates

Abbreviation: IE, infective endocarditis

In approximately 30% of patients with IE, a predisposing factor is recognized. A surgical or dental procedure can be implicated in approximately 65% of cases in which the potential source of bacteremia is identified. Poor dental hygiene in children with cyanotic heart disease results in a greater risk for endocarditis. Endocarditis from oral flora may occur without a preceding dental procedure. In these children, the occurrence of endocarditis directly after heart surgery is relatively low, but it is frequently an antecedent event.

PATHOGENESIS

The endothelial surface, initially injured by shearing forces caused by turbulent blood flow becomes susceptible to formation/deposition of noninfected thrombus comprising of fibrin, platelets and occasional red blood cells. Secondary bacteremia/fungemia in these children results in adherence of microbial pathogens to the injured endocardium and thrombus. Finally, fibrin and platelet deposition over the infected vegetation results in formation of a protective sheath that isolates the organisms from host defenses and permits rapid proliferation of the infectious agent. Subsequent involvement of other organs due to embolization or immune-mediated processes causes the complications of the disease.

MICROBIOLOGY

Infective endocarditis is also commonly referred to as bacterial endocarditis because bacteria are the predominant microbial pathogens; however, nonbacterial endocarditis can be caused by viruses, fungi, and other microbiological agents/microorganisms. It is believed that gram-positive cocci have a predilection for subendocardial connective tissue, especially fibronectin that gets exposed when endocardium is damaged. Viridans-type streptococci (α -hemolytic streptococci 20%) and *Staphylococcus aureus* (57%) are the leading causative agents responsible for endocarditis in children. *Escherichia coli* (2%), *Streptococcus pneumoniae* (1%), and *Haemophilus influenzae* (1%) are other bacterial microorganisms. Certain organisms are characteristically associated with some specific predisposing factors (**Table 3**).

Table 3 Characteristic organisms with specific predisposing factors

Commonly seen organism	Predisposing factors
<i>Staphylococcus aureus</i> IE	Native valves*
Viridans group streptococcal IE	Dental procedures
Group D enterococci IE	Lower bowel or genitourinary manipulation
Coagulase-negative staphylococci IE	Indwelling central venous catheter and use of high glucose concentrations parenteral nutrition especially in premature infants
<i>Pseudomonas aeruginosa</i> or <i>Serratia marcescens</i> IE	Intravenous drug users
Fungal IE [#]	Open heart surgery

* Presents as an acute fulminant process with a high mortality;

[#] Fungal IE vegetations are frequently large, rapidly increasing and friable with a tendency to embolize.

Abbreviation: IE, infective endocarditis.

Culture Negative Endocarditis

It is seen in 5–7% of children, although this incidence is higher in a series reported from India. The causes include previous administration of antimicrobial agents; inadequate microbiological techniques; infection with highly fastidious bacteria or nonbacterial pathogens; and filtering of bacteria originating from right-sided cardiac chambers, by the lungs.

CLINICAL FEATURES

Infective endocarditis in children has variable manifestations depending on the underlying cardiac disease and involvement of other organs secondary to embolization, the immunologic responses and virulence of the causative agent.

Subacute Presentation

Prolonged low-grade fever, fatigue, arthralgia, myalgia, weight loss, exercise intolerance, pallor, headache, diaphoresis and often microscopic hematuria, a feature of immunologically mediated glomerulonephritis are the usual presentations. A search for the peripheral stigmata of endocarditis, including evidence of small and large emboli with special attention to the fundi, conjunctivae, skin, and digits should be undertaken. Petechiae are present on the skin of the extremities or on mucous membranes such as the palate. Hemorrhages on the conjunctivae are usually seen on eversion of the eyelids. Splinter hemorrhages are nonblanching, linear, reddish-brown lesions found under the nail bed. Roth spots, Janeway lesions and Osler's nodes (features of vasculitis produced by circulating antigen-antibody complexes) are more specific findings of IE, though rare in children, must be looked for. Roth spots are exudative, edematous hemorrhagic lesions of the retina. Janeway lesions are macular, nonpainful, erythematous lesions on the palms and soles and Osler's nodes are painful, violaceous nodules found in the pulp of fingers and toes. Septic embolizations are not uncommon and result in small or major arterial occlusions with infective infarctions in extracardiac organs (e.g., osteomyelitis or pneumonia). The less virulent pathogens, such as *viridans* group streptococci and coagulase-negative staphylococci, are usually the causative agents for subacute IE.

Acute Infective Endocarditis

Acute IE has a progressive, fulminant course with features of high spiking fevers, rapidly changing symptoms and signs and deteriorating cardiac functions with cardiogenic shock

necessitating urgent, aggressive and appropriate therapy. It has rapid destruction of heart valve tissue, abscess formation and embolic phenomena responsible for the hyperacute clinical presentation and hence is associated with significant morbidity and high mortality. *S. aureus* is the usual causative agent.

Right-sided cardiac lesions are noted in patients with native endocarditis or catheter-related IE. They may have few or no specific cardiovascular signs but may present with primarily pulmonary symptoms and signs secondary to septic pulmonary embolization.

The symptoms and signs of IE in children are listed in **Table 4**. Splenomegaly, septic emboli to skin (petechiae or purpuric rashes), microscopic hematuria and a high C-reactive protein (CRP) value of more than 100 mg/L are important clues to the diagnosis of IE as reported by Liew et al.

Neonatal Infective Endocarditis

In neonates, the signs and symptoms of IE are nonspecific. They include feeding intolerance, tachycardia, respiratory distress, hypotension, and a new or changing murmur. Fever may be absent and persistently positive blood cultures may be the only clue to diagnosis. Fungal IE is more common in the neonates and may present as acute fulminant course with septicemia or heart failure.

DIAGNOSIS

The diagnosis of IE is based on the history, physical examination, blood culture, laboratory results, and an echocardiogram. The modified Duke criteria is the most commonly used among several available diagnostic criteria for IE.

Duke Criteria

The modified Duke criterion is divided into major and minor findings. The clinical diagnosis of definitive IE requires the presence of either two major criteria, one major and three minor criteria, or five minor criteria (**Tables 5 and 6**).

- **Major clinical criteria** (1) Positive blood cultures (two separate cultures for a usual pathogen, two or more for less typical pathogens); and (2) Echocardiographic: Evidence of endocarditis (intracardiac mass on a valve or other sites, regurgitant flow near a prosthesis, abscess, partial dehiscence of prosthetic valves, or new valve regurgitant flow).
- **Minor clinical criteria** Predisposing conditions, fever, embolic-vascular signs, immune complex phenomena (glomerulonephritis, arthritis, rheumatoid factor, Osler nodes, and Roth spots), a single positive blood culture or serologic

Table 4 Presenting symptoms and signs in children with infective endocarditis (IE)

Symptoms	Signs
<ul style="list-style-type: none"> • Fever • Chills • Chest and abdominal pain • Arthralgia, myalgia • Dyspnea • Malaise • Night sweats • Weight loss • CNS manifestations (stroke, seizures, headache) 	<ul style="list-style-type: none"> • Elevated temperature • Tachycardia • New or changing murmur • Embolic phenomena (Roth spots, petechiae, splinter nail bed hemorrhages, Osler nodes, CNS or ocular lesions) • Janeway lesions • Splenomegaly • Arthritis • Heart failure • Arrhythmias • Metastatic infection (arthritis, meningitis, mycotic arterial aneurysm, pericarditis, abscesses, septic pulmonary emboli) • Clubbing

Table 5 Modified Duke criteria for diagnosis of infective endocarditis (IE)

Major criteria
<ol style="list-style-type: none"> Positive blood culture for IE <ol style="list-style-type: none"> Typical microorganism consistent with IE from two separate blood cultures as follows: <ol style="list-style-type: none"> Viridans streptococci, <i>Streptococcus bovis</i>, or HACEK group or Community acquired <i>Staphylococcus aureus</i> or enterococci, in the absence of a primary focus or Microorganisms consistent with IE from persistently positive blood cultures defined as <ol style="list-style-type: none"> More than two positive cultures of blood samples drawn > 12 hours apart or All of three or a majority of four separate cultures of blood (with first and last sample drawn > 1 hour apart) Evidence of endocardial involvement <ol style="list-style-type: none"> Positive echocardiogram for IE defined as <ol style="list-style-type: none"> Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation, or Abscess, or New partial dehiscence of prosthetic valve or New valvular regurgitation (worsening or changing of pre-existing murmur not sufficient)
Minor criteria
<ol style="list-style-type: none"> Predisposing heart condition or IV drug use Fever: Temperature > 38°C Vascular phenomena: Major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway lesions Immunologic phenomena: Glomerulonephritis, Osler nodes, Roth's spots, and rheumatoid factor Microbiological evidence: Positive blood culture but does not meet a major criterion as noted earlier or serological evidence of active infection with organism consistent with IE Echocardiographic findings: Consistent with IE but do not meet a major criterion as noted earlier
Definite Infective Endocarditis
<ul style="list-style-type: none"> Pathologic evidence of intracardiac or embolized vegetation or intracardiac abscess OR Clinical criteria: Two major, or one major and three minor, or five minor criteria
Possible Infective Endocarditis
<ul style="list-style-type: none"> One major and one minor or three minor criteria
Rejected
<ul style="list-style-type: none"> Firm alternate diagnosis <i>IE syndrome</i> resolved within 4 days of antibiotic therapy No pathologic evidence of IE at surgery or autopsy within 4 days of antibiotic therapy

Table 6 Complications of infective endocarditis

• Congestive heart failure
• Pericarditis
• Cardiac valvular insufficiency
• Embolic events, e.g., cerebral, pulmonary, renal, coronary (Stroke syndromes)
• Persistent bacteremia or fungemia
• Periannular extension of abscess, Sinus of Valsalva aneurysm and intracardiac fistula
• Prosthetic device dysfunction including valvular dehiscence
• Arrhythmia or development of new heart block
• Aortic root or myocardial abscesses
• Mycotic aneurysms
• Glomerulonephritis/acute renal failure
• <i>Metastatic abscess:</i> Mesenteric or splenic abscess or infarct

evidence of infection, and echocardiographic signs not meeting the major criteria.

Despite the above criteria, IE remains a clinical diagnosis and a high index of suspicion is warranted in any child at risk for IE (those with pre-existing heart disease or indwelling central venous catheter) in the presence of fever without a focus.

Laboratory Tests

Culture Collection

Blood cultures provide the critical information for institution of appropriate treatment of IE. All others are secondary in

importance. As bacteremia in IE is usually continuous, it is not necessary to obtain the cultures during fever only. Routinely, three blood cultures (2–3 mL of blood) under strict aseptic precautions are recommended in children. In 90% of cases of endocarditis, the causative agent is recovered from the initial two blood cultures. If there is no growth by 2nd day, two more blood cultures may be drawn in case antibiotics have not been started. Unless otherwise suspected, blood cultures are usually performed for aerobic organisms. Delayed cultures especially on enriched media are necessary to detect fastidious bacteria or fungi.

Each set of cultures should be obtained from separate venipuncture sites, and ideally blood cultures should not be obtained from a vascular catheter. If the patient is not acutely ill, antibiotic therapy can be withheld for 24–48 hours while the blood cultures are obtained. The diagnostic yield is better in the absence of recent antimicrobial therapy.

Interpreting Culture Results

The Duke criteria for the diagnosis of endocarditis define certain organisms as *typical causes* of IE (**Table 5**). The risk of endocarditis in patients with *S. aureus* bacteremia is particularly high. False-positive cultures are due to contamination during blood collection and present a special problem, as bacteria found on the skin may also themselves cause IE. *Propionibacterium acnes*, *Corynebacterium* spp., *Bacillus* species, and coagulase-negative staphylococci are the usual pathogens. The probability of pathogenicity is increased if the organism is observed in multiple blood cultures obtained by independent venipunctures.

Culture-negative Endocarditis

It should be considered in patients with negative blood cultures and persistent fever with one or more clinical findings consistent with infective endocarditis (IE) (e.g., stroke or other manifestations of emboli) and/or those with echo-demonstrated vegetations. In children with persistent fever and suspected IE, serologic diagnosis is necessary to detect unusual or fastidious microorganisms like *Coxiella burnetii*, *Bartonella* spp., *Chlamydophila* spp., *Legionella* spp., and *Brucella*.

Echocardiography

Echocardiography has a key role in the diagnosis of IE. An echocardiogram should be performed on all patients in whom there is a reasonable suspicion of IE, as it may detect the presence of a vegetation; a major diagnostic Duke criterion (**Table 5**). It helps to demonstrate the vegetation (**Figs 1 and 2**), presence and severity of valvar destruction, assesses the degree of valvar regurgitation, predict embolic complications (lesions greater than 1 cm and fungating masses are at greatest risk for embolization) and presence of complications like paravalvar leak, myocardial abscess, etc., are echo findings considered to represent *Major Duke Criteria*. Other abnormal echocardiographic findings not fulfilling the definitions are considered as minor criteria.

The diagnostic yield of echocardiography is influenced by the image quality, size of vegetation, (vegetation < 2–3 mm may not be well seen), location of vegetation (e.g., vegetation on a

prosthetic valve are difficult to visualize) and experience of the echocardiographer. Transthoracic echocardiography (TTE) is more sensitive in children than in adults due to better acoustic windows. Indications for transesophageal echocardiography (TEE) in children are in select conditions and include:

- Inadequate TTE imaging as in overweight or muscular children
- Those with high clinical suspicion of IE and a negative TTE
- Children with significant respiratory disease that limits TTE
- Children with complex congenital heart disease (CHD)
- Status postrepair as artifacts from prosthetic material (grafts and conduits) and valves which may interfere with TTE imaging
- Aortic valve endocarditis or aortic root abscess on TTE
- Paravalvar damage and valve dehiscence due to prosthetic valve infection
- Right-sided vegetations.

The limitations of echocardiography are: (1) False negative results with small vegetations or in embolized vegetations; (2) not all echogenic masses are necessarily vegetations; and (3) inability to differentiate active vegetation from an old sterile vegetation. Once treatment is completed, a repeat evaluation may be necessary to establish a new baseline of valvar and myocardial functions for the patient.

Other Tests

Hemoglobin is low. Erythrocyte sedimentation rate (ESR) and CRP are elevated. Urinalysis shows hematuria, proteinuria, and red cell casts suggestive of glomerulonephritis. ECG may reveal a first degree or complete heart block which suggests vegetations with periannular extension. Magnetic resonance imaging (MRI) of the brain may be useful in children with definite or suspected IE with neurological symptoms.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes an alternate source of infection in a bacteremic patient with underlying heart disease, skin and soft tissue infection, cardiac device infection, intravascular catheter infection, musculoskeletal infection, meningitis and pneumonia. Other illnesses in children with overlapping symptoms and signs as seen in IE, include blood malignancies, collagen-vascular disease, Kawasaki disease, myocarditis, rheumatic fever and vasculitis.

MANAGEMENT

The principles of management of IE in children are antimicrobial therapy, timely surgical intervention in selected cases and monitoring for complications.



Figure 1 Two-dimensional (2D) echocardiogram showing aortic valve endocarditis

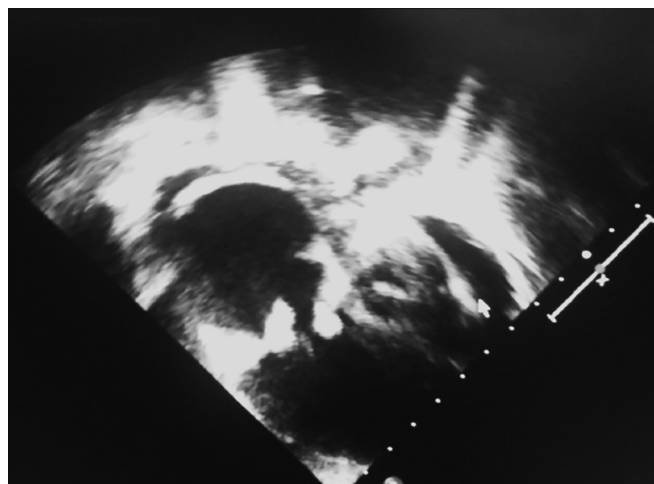


Figure 2 Two-dimensional (2D) echocardiogram showing vegetations on tricuspid valve (native endocarditis)

Antimicrobial Therapy

Antibiotics being the mainstay of treatment for IE, their choice, dosage, and duration of treatment are dependent upon the underlying causative microbial agent's identity and susceptibility. There are minor differences, in recommended treatment guidelines for specific microorganism, amongst the American Heart Association (AHA), British Society for Antimicrobial Chemotherapy (BSAC), and the European Society for Cardiology (ESC). Bactericidal antibiotics should be started empirically after blood cultures are collected, if the patient is acutely ill. However, if the child is stable, it would be advisable to wait for 48 hours till antibiotic sensitivity testing is carefully reviewed. If cultures are negative two additional cultures should be done.

Empiric Antibiotic Treatment

It is generally directed to the most common pathogens, i.e., streptococci, staphylococci and enterococci. The chosen antibiotics must be given intravenously to attain persistently high bactericidal concentrations. Duration of therapy in patients with native valve endocarditis ranges from 2 weeks to 6 weeks, depending on the pathogen and site of valvar infection. Infection of prosthetic valves and tissue, infection with highly virulent or more resistant pathogens may require longer treatment usually 6–8 weeks. Prolonged therapy is often necessary to eradicate organisms that are growing in relatively inaccessible avascular vegetation. Guidelines recommended by AHA are summarized as follows:

1. *Penicillin-susceptible streptococcal endocarditis (PSSE) on native cardiac valve* Penicillin G for 4 weeks or penicillin or ceftriaxone combined with gentamicin for 2 weeks.
2. *Penicillin-resistant streptococcal endocarditis (PRSE) on native cardiac valves* Penicillin, or ampicillin, or ceftriaxone for 4 weeks, combined with gentamicin for the first 2 weeks.
3. *PSSE on a prosthetic valve or other prosthetic material* Penicillin G or ampicillin, or ceftriaxone for 6 weeks, combined with gentamicin for the first 2 weeks.
4. *PRSE on a prosthetic valve or other prosthetic material* Penicillin G or ampicillin, or ceftriaxone for 6 weeks, combined with gentamicin for the first 2 weeks; vancomycin can be used in patients who cannot tolerate penicillin or ceftriaxone. The duration of penicillin-resistant therapy for streptococcal endocarditis on a prosthetic valve is 6 weeks.
5. *Susceptible enterococcal infection on native valves* Penicillin or ampicillin, combined with gentamicin, for 4–6 weeks.
6. *Susceptible enterococcal infection on prosthetic material* should be treated for at least 6 weeks.
7. *Methicillin-susceptible S. aureus (MSSA) infection on native valves* Nafcillin or oxacillin for at least 6 weeks with 3–5 days of optional gentamicin.
8. *Methicillin-resistant S. aureus (MRSA) infection on native valves* Vancomycin for at least 6 weeks, with or without 3–5 days of gentamicin.
9. *MSSA infection on prosthetic tissue* Nafcillin or oxacillin plus rifampin for at least 6 weeks, in combination with gentamicin for 2 weeks.
10. *MRSA infection on prosthetic tissue* Vancomycin plus rifampin for at least 6 weeks, in combination with gentamicin for 2 weeks.
11. *Gram-negative endocarditis caused by HACEK organisms* Ceftriaxone or ampicillin plus gentamicin for 4 weeks.

Linezolid or daptomycin are options for patients with intolerance to vancomycin or resistant organisms. Substitution of linezolid for vancomycin should also be considered in patients

with unstable renal function because of the difficulty of achieving therapeutic trough levels. Repeat blood cultures and ESR may be necessary to assess complete response though clinical response is often sufficient. Use of recombinant tissue plasminogen activator to lyse intracardiac vegetations in severely ill infants has been mentioned in literature. Digitalis, salt restriction, diuretic therapy and other standard protocol should be instituted in supportive care of heart failure.

Fungal Endocarditis

Intravenous amphotericin B is the first-line antifungal therapy for IE in children. Renal parameters must be monitored closely, as it is highly nephrotoxic. Duration of therapy is prolonged and generally for 6–8 weeks, followed by oral antifungal agents like fluconazole. The total duration of treatment for eradication may be 1 year or more. 5-fluorocytosine may have an additive effect when combined with amphotericin B. However, the superiority of two drug combination over amphotericin B alone has not been proven by randomized trial. Medical therapy alone is often not successful and surgical intervention is often necessary.

Surgical Intervention

Surgical intervention should be contemplated early if the likely result is more favorable than with medical management, based upon an echo-guided analysis of the relative risks and benefits. About one-fifth of patients require surgery in acute phase. The goals of surgery are to eradicate the focus of infection, to repair cardiac defects and to prevent development of complications. Indications for surgery during the acute phase of IE are:

- Continued bacteremia or persistent fever after 2 weeks of appropriate antibiotic therapy
- Worsening heart failure due to valvar regurgitation
- Embolic events; systemic, pulmonary, coronary, or cerebral
- Myocardial or periannular abscess
- Pathogens those are difficult to cure with medical therapy alone like *Pseudomonas aeruginosa*, *Brucella*, and fungal endocarditis
- *Leaflet perforation*, or sinus of Valsalva aneurysm
- Mobile vegetations more than 10 mm in the setting of severe valve regurgitation or stenosis
- Prosthetic valve dysfunction like valve dehiscence.

Postoperatively, a full course of antimicrobial therapy starting from the time of surgery is warranted and at times antibiotics changed according to culture sensitivity of organisms grown on operative valve/tissue cultures. Late surgery may be indicated in some patients after the IE has been controlled, e.g., in a patient with small ventricular septal defect with a previous episode of IE.

COMPLICATIONS

Despite the use of antibiotic agents, mortality remains at 20–25%. Serious morbidity occurs in 50–60% of children with documented IE. Complications can occur before, during, and after completion of therapy. Cardiac complications include cardiac failure, perivalvar abscess, pericarditis, and intracardiac fistula. Congestive heart failure can occur secondary to ruptured leaflets or chordae and is the most common cause of death. Development of a new onset heart block may suggest perivalvar extension of infection. Large (> 10 mm), mobile vegetations are more likely to embolize. Embolization can occur even up to 2–4 weeks after starting antibiotic therapy. Metastatic infection due to septic emboli may result in septic arthritis, vertebral osteomyelitis, and pneumonia,

distal abscesses in the kidneys, spleen, brain or soft tissues. Septic emboli can occlude or damage any vessel in the systemic or pulmonary arterial circulation. More than one complication can occur simultaneously (**Table 6**).

Risk factors for IE complications include prosthetic cardiac valves; left-sided valvar involvement; *S. aureus* or fungal IE; previous IE; prolonged symptoms more than or equal to 3 months; complex cyanotic CHD; systemic-to-pulmonary shunts, conduits, or other prostheses; poor clinical response to antimicrobial therapy; and prematurity.

PROPHYLAXIS

Though antibiotic prophylaxis was being practiced for many decades to prevent IE, evidence to support antimicrobial prophylaxis as an effective preventive measure is weak and inconclusive. Also the risk of antibiotic-associated adverse events exceeds the benefit. For these reasons, AHA in 2007 simplified its recommendations—guidelines for the prevention of IE in children. Today, antibiotic prophylaxis is given only to those who are at the highest risk for IE (**Table 7**).

These guidelines emphasize that IE is much more likely to result from frequent exposure to random bacteremia associated with daily activities than from bacteremia caused by a dental, gastrointestinal (GI) tract or genitourinary (GU) tract procedures. Thus, now there is a great emphasis on maintaining good orodental hygiene as poor dental hygiene is responsible for a large proportion of IE cases. Following highest risk procedures may result in transient bacteremia:

- All dental procedures that involve manipulation of either gingival tissue or the periapical region of teeth or perforation of the oral mucosa would warrant antibiotic prophylaxis. Routine anesthetic injections through noninfected tissue, taking dental radiographs, placement or adjustments of removable prosthodontic or orthodontic appliances, and bleeding from trauma to the lips or oral mucosa *do not* require IE prophylaxis
- Procedures of the respiratory tract that involve incision or biopsy of the respiratory mucosa
- Procedures in patients with ongoing GI or GU tract infection
- Procedures on infected skin, skin structure, or musculoskeletal tissue
- Surgery to place prosthetic heart valves or prosthetic intravascular or intracardiac materials.

Table 8 Regimen of antibiotic prophylaxis prior to dental procedures

Situation	Agent	Regimen: Single dose 30–60 min before procedure Dose/kg (maximum dose/adult dose)
Oral	Amoxicillin	50 mg/kg (2 g)
Unable to take oral medication	Ampicillin or Cephazolin or Ceftriaxone	50 mg/kg IM or IV (2 g) 50 mg/kg IM or IV (1 g)
Allergic to penicillin or ampicillin (Oral)	Cephalexin or Clindamycin or Azithromycin or Clarithromycin	50 mg/kg (2 g) 20 mg/kg (600 mg) 15 mg/kg (500 mg)
Allergic to penicillins or ampicillin and unable to take oral medication	Cephazolin or Ceftriaxone or Clindamycin phosphate	50 mg/kg IM or IV (1 g) 20 mg/kg IM or IV

The choice of antibiotic is patient and procedure specific (**Table 8**) and have to be administration only once, 30–60 minutes prior to the procedure. The applicability of these guidelines in India is not very clear. Hence, good orodental health should be addressed to the patient/parent during each follow-up visit.

MORE ON THIS TOPIC

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Table 7 Indications for prophylaxis against infective endocarditis in patients undergoing dental procedures

Prophylaxis indicated	Prophylaxis not indicated
<ul style="list-style-type: none"> • Prosthetic cardiac valves • Previous infective endocarditis • Unrepaired cyanotic CHD, including palliative shunts and conduits • Completely repaired CHD with prosthetic material or device, during the first 6 months after the procedure • Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialization) • Cardiac transplant recipients with cardiac valvulopathy • RHD if prosthetic valves or prosthetic material used in valve repair 	<ul style="list-style-type: none"> • Atrial septal defects • Ventricular septal defects • Patent ductus arteriosus • Mitral valve prolapse • Previous Kawasaki disease • Hypertrophic cardiomyopathy • Previous coronary artery bypass graft surgery • Cardiac pacemakers (intravascular and epicardial) and implanted defibrillators • Bicuspid aortic valves • Coarctation of the aorta • Calcified aortic stenosis • Pulmonic stenosis

Abbreviations: RHD, rheumatic heart disease; CHD, congenital heart disease.

IN A NUTSHELL

1. Infective endocarditis (IE) is a serious infection, associated with significant morbidity and mortality and is increasingly being recognized in children and adolescents.
2. Most children with IE have an identifiable risk factor for the disease. IE should be part of the differential diagnosis of a persistent febrile or inflammatory illness, particularly if there are pre-existing cardiac lesions.
3. The diagnosis of IE is based on clinical findings, positive blood cultures, laboratory results, and an echocardiogram. The modified Duke criterion is the most commonly used among several available diagnostic criteria for IE.
4. The principles of management of IE in children are prolonged antimicrobial therapy, timely surgical intervention in selected cases and monitoring for complications.
5. Despite the use of antibiotic agents, serious morbidity occurs in 50–60% and mortality in 20–25%. Complications can occur before, during, and after completion of therapy.

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Chapter 40.35

Myocardial Diseases:
Myocarditis and
Cardiomyopathies

Ronak Naik, Nishant Shah

MYOCARDITIS

Myocarditis refers to myocardial inflammation caused by various infectious and noninfectious agents and is pathologically characterized by inflammatory cell infiltrates and myocyte necrosis or degeneration. Myocarditis can be acute or chronic.

ETIOLOGY

In the past, many cases of myocarditis remained undiagnosed because of its insidious onset of the disease process, benign course and lack of sophisticated virological identification techniques. Viral infections got identified as the most common cause of proven myocarditis in older children and adults by endomyocardial biopsy (EMB). It remained difficult to prove the viral etiology in acute myocarditis and acute onset dilated cardiomyopathy (DCM) cases in infants and young children because of infrequent use of this invasive procedure. With the development of new molecular techniques such as polymerase chain reaction (PCR) and in situ hybridization, it is possible to identify the viral genome responsible for myocarditis.

Recent literatures suggest that parvovirus B19 and human herpesvirus 6 are more commonly identified in patients with myocarditis, compared to enterovirus and adenovirus in the 1990s and early 2000s. Common infectious and noninfectious causes of myocarditis are listed in **Table 1**.

PATHOPHYSIOLOGY

In the acute or early phase, viral infection of myocytes occurs, resulting in viral replication; cytolysis of infected myocyte soon follows from direct injury. In the subacute phase, activation of cell-mediated immunity, while trying to clear the viral infection, further aggravates the myocardial damage from cell-mediated cytotoxicity. In a subset of patients, chronic perpetuation of myocardial inflammation leads to ongoing myocardial damage. Viral persistence and autoimmunity with or without genetic predisposition have been widely speculated to be responsible for the sequelae.

Flow chart 1 shows the pathophysiologic sequences in myocarditis and its progression to DCM.

Mumps and coxsackievirus B3 have been identified in the myocardium of infants with endocardial fibroelastosis. Coronary insufficiency is common with parvovirus B19 myocarditis in children. Arrhythmias including complete heart block are frequent complications of diphtheritic myocarditis. Giant cell myocarditis (GCM) is a rare but severe form of myocarditis characterized by the presence of multinucleated giant cells and extensive myocardial necrosis. It is thought to be autoimmune in origin.

CLINICAL FEATURES

Myocarditis has wide spectrum of presentation, from subclinical disease to life-threatening events such as cardiogenic shock and significant arrhythmias. In children, presentation depends

Table 1 Causes of myocarditis

Infections	
RNA viruses	Coxsackievirus A and B, echovirus, mumps virus, measles virus, rubella virus, hepatitis C virus, respiratory syncytial virus, influenza A and B virus, human immunodeficiency virus-1
DNA viruses	Parvovirus B19, human herpes virus-6, cytomegalovirus, adenovirus, Epstein-Barr virus, varicella virus, herpes simplex virus
Bacterial	Mycoplasma, Staphylococcus and Streptococcus spp. Corynebacterium diphtheriae, Salmonella typhi, mycobacteria
Rickettsial	Coxiella burnetti, Rickettsia typhi
Spirochetal	Borrelia burgdorferi, Leptospira
Fungal	Candida, Aspergillus, Cryptococcus
Parasitic	Echinococcus granulosus, Trichinella spiralis
Protozoal	Toxoplasma gondii, Trypanosoma cruzi
Noninfectious causes	
Autoimmune	Kawasaki disease, rheumatic fever, systemic lupus erythematosus, rheumatoid arthritis, celiac disease, Churg-Strauss syndrome, Crohns disease, ulcerative colitis, dermatomyositis, giant cell myocarditis, hypereosinophilic syndrome
Toxic	Drugs: Anthracyclines, cyclophosphamide, 5-fluorouracil, catecholamines, cocaine, amphetamines Metals: Copper, iron, arsenic, lead Physical agents: Radiation Hormones: Pheochromocytoma Other: Ethanol
Hypersensitivity	Penicillin, ampicillin, cephalosporins, tetracyclines, sulfonamides, antiphlogistics, benzodiazepines, clozapine, loop and thiazide diuretics, methyl dopa, tetanus toxoid, tricyclic antidepressants

Abbreviations: RNA, ribonucleic acid; DNA, deoxyribonucleic acid.

on the age. Newborns and infants can have feeding difficulties, vomiting, irritability, pallor and respiratory distress. Older children and adolescents can present with poor appetite, low-grade fever, general malaise, chest pain, palpitation and exercise intolerance.

Physical examination is consistent with signs of congestive heart failure such as tachypnea, tachycardia, poor peripheral circulation, hepatomegaly, gallop (S₃) and holosystolic murmur from mitral regurgitation.

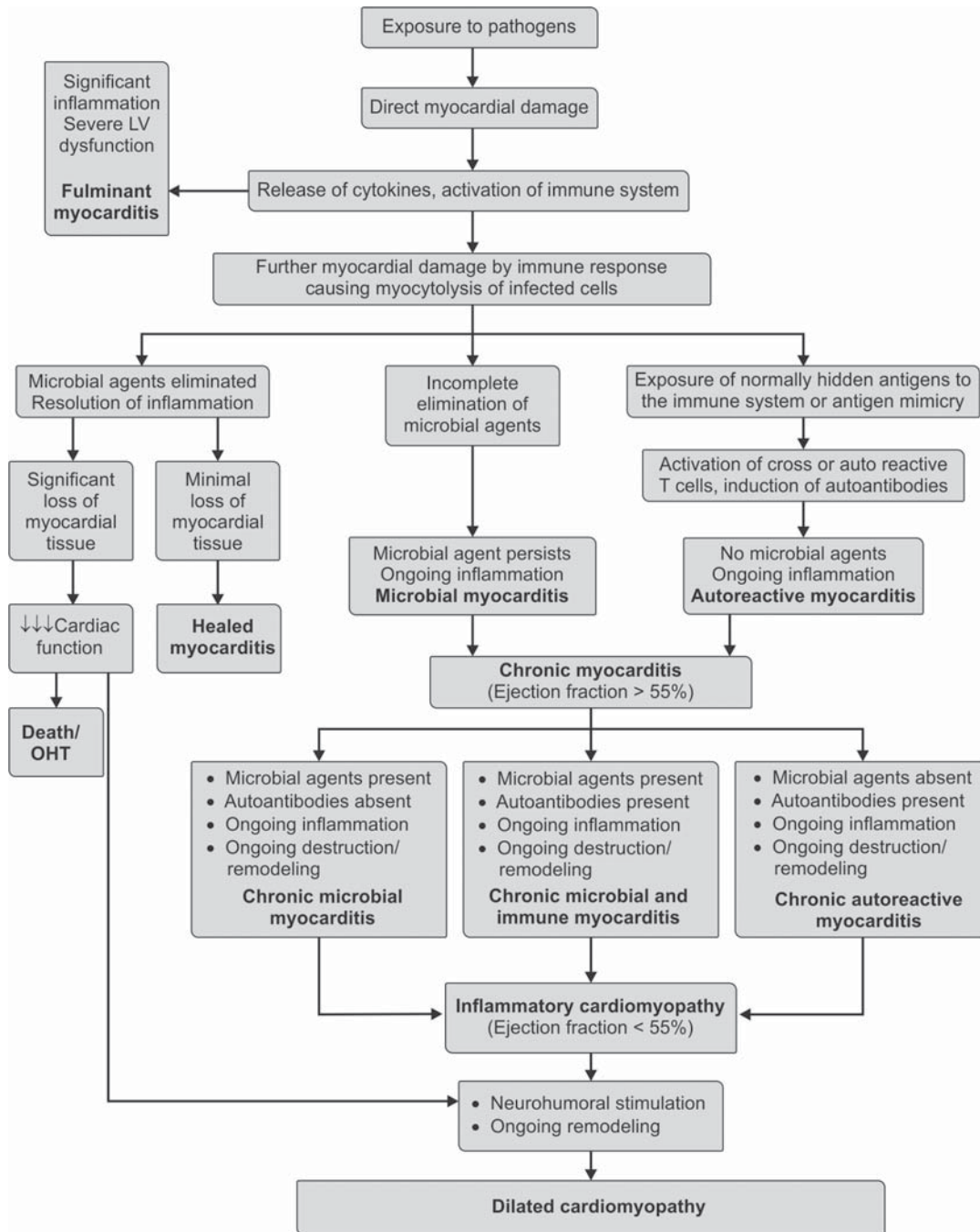
DIAGNOSIS

Electrocardiography

Findings include sinus tachycardia, low voltage QRS complex, ST elevation, T wave inversion and nonspecific T wave changes; however these findings are not sensitive and specific for myocarditis. Various arrhythmias such as ventricular tachycardia, atrial fibrillation, supraventricular tachycardia and atrioventricular (AV) block may occur.

Echocardiography

Assessment of myocarditis with evaluation of chamber size and wall thickness, ventricular function (systolic as well as diastolic), regional wall motion abnormalities, valvar (i.e., mitral) regurgitation and pericardial effusion are all possible with echocardiography.

Flow chart 1 Pathophysiology of myocarditis and dilated cardiomyopathy

Abbreviation: OHT, orthotopic heart transplantation.

Cardiovascular Magnetic Resonance Imaging

Cardiovascular magnetic resonance imaging (CMR) has greatly enhanced our ability to characterize myocardial inflammation. In addition to volume and functional data, information on myocardial edema (T2 weighted images), hyperemia (T1 weighted contrast enhanced images) and area of necrosis and fibrosis from late gadolinium enhancement is very useful to diagnose active inflammation.

Endomyocardial Biopsy

It is considered as the gold standard to diagnose myocardial inflammation. EMB however being invasive carries a small but measurable risk of myocardial perforation or the development of

untoward hemodynamic or arrhythmic events in children during the catheterization and biopsy. Involvement of myocardium often is patchy and scattered which reduces the sensitivity of EMB to diagnose myocarditis. For all these reasons, many centers do not perform EMB routinely in children with suspected myocarditis. When used, EMB should be performed by an experienced team, and tissue obtained from EMB should be analyzed using histology, immunochemistry and viral PCR.

Based on the Dallas criteria, myocarditis can be classified as active, borderline or no myocarditis, depending on the presence of an inflammatory infiltrate with (active) or without (borderline) myocyte degeneration or necrosis.

Others

Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and brain natriuretic peptide levels are often raised in myocarditis. 35–45% of EMB-proven myocarditis cases have elevated troponin.

Viral culture from various specimens such as blood, stool or urine is commonly performed but is unreliable in identifying the causative infection.

Viral serology often leads to incorrect diagnosis because of the high prevalence of IgG antibodies in the general population and positive serology does not confirm myocardial infection.

MANAGEMENT

Treatment of myocarditis depends on the severity of illness and presenting symptoms. Standard heart failure therapy should be initiated according to the New York Heart Association (NYHA) functional class.

Diuretics help the children with breathing difficulties and congestion. *Angiotensin-converting-enzyme (ACE) inhibitors* and *angiotensin II receptor blockers (ARBs)*—afterload reducing agents should be considered in children with decreased left ventricular function. Use of *intravenous immunoglobulin (IVIG)* in children with acute myocarditis has shown improvement of left ventricular function in one study; however, there was no benefit from IVIG in adult patients with myocarditis compared to placebo. Nevertheless, IVIG has no major side effects and may be used in myocarditis in children. Treatment with *immunosuppressive agents* such as cyclosporine, prednisolone and azathioprine in acute myocarditis remains controversial. Infectious disease specialists should be consulted while considering the use of specific *antiviral therapies*, including use of interferon. Extracorporeal membrane oxygenation (ECMO) and/or a mechanical cardiopulmonary assist device may be needed as a bridge to recovery or to heart transplantation in patients with hemodynamic instability.

Follow-up

After resolution of the clinical presentation (at least 6 months after the onset of the disease), clinical reassessment is indicated before the child resumes competitive sport. All patients with myocarditis should be followed with clinical assessment, electrocardiography (ECG), and echocardiography.

PROGNOSIS

The outcome of myocarditis depends on age at the time of presentation, etiology and presence or absence of ventricular dysfunction. Neither the severity of inflammation nor the detection of viral genome has been shown to be a predictor of poor outcome. Nearly 50% of cases resolve without long-term complications. However, newborns and infants have a significantly higher mortality rate compared to older children and adolescents (75% vs. 10–25%) diagnosed with myocarditis.

CARDIOMYOPATHIES

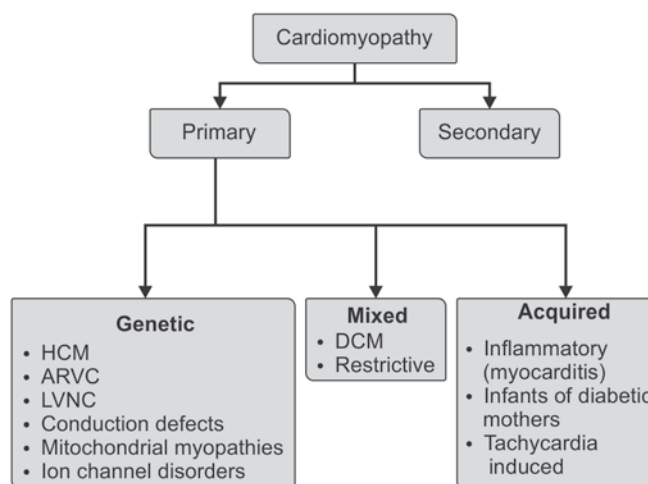
Cardiomyopathies refer to a heterogeneous group of diseases of the myocardium associated with mechanical and/or electrical dysfunction, usually exhibiting inappropriate ventricular hypertrophy or dilatation. Though they are of varied causes, mostly they are genetic.

CLASSIFICATION

Cardiomyopathies are classified into two major groups (**Flow chart 2**).

1. *Primary cardiomyopathies* Here, the disease state is solely or predominantly confined to myocardium. Hypertrophic

Flow chart 2 Classification of cardiomyopathies



Abbreviations: DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; ARVC, arrhythmogenic right ventricular cardiomyopathy; LVNC, left ventricular noncompaction.

cardiomyopathy (HCM) and DCM resulting from genetic mutations are examples of primary cardiomyopathies. Primary cardiomyopathies are further divided into genetic, mixed (genetic and nongenetic) and acquired.

2. *Secondary cardiomyopathies* Myocardial involvement is part of generalized systemic disorders involving other organ systems. HCM in Noonan syndrome and DCM in neuromuscular disorders such as Duchenne muscular dystrophy are the examples. The mixture of morphology and physiology inherent within this classification can lead to overlapping cases.

DILATED CARDIOMYOPATHY

Prevalence

Dilated cardiomyopathy is the most common form of cardiomyopathy in children with a prevalence of 36.5 per 100,000, needing early heart transplantation. In Asian populations the incidence is 1.9–3.6 per 100,000 person-years. Cardiac dilatation with decreased systolic function is the unique feature of DCM.

Etiology

Various primary and secondary causes of DCM (**Table 2**) leading to myocardial damage share similar phenotypic clinical presentations. In children, up to two-thirds cases of DCM are idiopathic. The most common known causes of DCM are myocarditis, neuromuscular disorders and familial DCM. About 20–50% of DCM patients have a familial form of the disease caused by more than 37 genetic mutations (**Figure 1**), the most common being mutations in TTN (titin), MYH7 (beta-myosin heavy chain) and MYH6 (alpha-myosin heavy chain) gene.

Pathophysiology

In DCM, all the four cardiac chambers are dilated with atrial dilation in proportion to ventricular dilation resulting characteristically in progressive impairment of systolic performance of the ventricles. Compensatory neurohumoral activation mechanisms are able to restore cardiovascular function to a normal homeostatic range for a short period of time. However, with time the sustained activation of these systems can lead to secondary end-organ damage within the ventricles, worsening left ventricle (LV) remodeling (chronic myocyte death, increased myocardial mass from interstitial fibrosis, and ventricular dilation and wall thinning due to slippage

Table 2 Etiology of primary and secondary dilated cardiomyopathy

Idiopathic	Two-thirds cases
Familial	Autosomal dominant (most common), X-linked, autosomal recessive, mitochondrial
Myocarditis	Acute or chronic (described in detail elsewhere)
Neuromuscular disease	Muscular dystrophies (Duchenne's, Becker, limb-girdle, Emery-Dreifuss), myotonic dystrophy, Friedreich's ataxia, tuberous sclerosis, neurofibromatosis
Infection	Viral, bacterial, fungal, parasitic, rickettsial, spirochetal (detailed in myocarditis section)
Nutritional	Beriberi (thiamine), pellagra, scurvy, selenium, carnitine, kwashiorkor
Drugs	Anthracyclines, sympathomimetics, antiretroviral agents, cyclophosphamide, radiation therapy
Endocrine	Thyroid disorders, hypoparathyroidism, pheochromocytoma, diabetes, acromegaly
Metabolic	Glycogen storage diseases, mucopolysaccharidoses, mitochondrial disorders, organic acidemias (propionic), fatty acid oxidation disorders, carnitine transport disorders, hemochromatosis, amyloidosis
Ischemic	Atherosclerosis, Kawasaki disease, anomalous origin of the left coronary artery from pulmonary artery (ALCAPA)
Chronic arrhythmias	Atrial and ventricular
Collagen vascular disease or autoimmune diseases	Systemic lupus erythematosus, rheumatoid arthritis, dermatomyositis, polyarteritis nodosa
Toxins	Cobalt, lead
Others	Systemic hypertension, peripartum

of aligned myocytes) and subsequent cardiac decompensation (**Figs 2A and B**). Current heart failure treatment is targeted to reverse or reduce this maladaptive remodeling.

Clinical Features

Dilated cardiomyopathy usually has insidious onset. Superimposed respiratory infection may result in acute decompensation. A history of preceding viral illness is not uncommon in acquired forms of DCM secondary to myocarditis. A detailed family history is important and is positive in 20–48% of cases of DCM. Presenting symptoms and physical findings are described in **Table 3**. The diagnostic investigative work-up and findings of DCM are described in **Table 4**.

Prognosis

Dilated cardiomyopathy is the most common cause of heart transplantation in adult and children. The reported 1 year and 5 year survival rates in idiopathic DCM are 63–90% and 20–80%. The prognostic predictors of survival are given in the **Table 5**.

Management

The treatment objectives of the DCM:

- To treat congestive heart failure
- To treat/prevent arrhythmia
- To treat/prevent thromboembolic complications
- To correct underlying etiology.

The anticongestive therapy addresses increased fluid retention, low cardiac output and increased peripheral vasoconstriction. Treatment is described in **Tables 6 and 7**.

HYPERTROPHIC CARDIOMYOPATHY

The past nomenclature for HCM includes idiopathic hypertrophic subaortic stenosis (IHSS) or hypertrophic obstructive cardiomyopathy (HOCM). HCM is now a widely accepted term and it includes both, obstructive and nonobstructive forms of HCM.

HCM is a disease state characterized by unexplained left ventricular hypertrophy (LVH) associated with nondilated

ventricular chambers in the absence of another cardiac or systemic disease being entirely responsible for the magnitude of hypertrophy evident in a given patient.

Clinically, HCM is usually recognized by maximal LV wall thickness more than or equal to 15 mm, with wall thickness of 13–14 mm considered borderline, particularly in the presence of other compelling information (e.g., family history of HCM). In children, increased LV wall thickness in HCM is defined as wall thickness more than or equal to 2 SD (SD = standard deviation) above the mean (Z score ≥ 2) for age, sex, or body size.

Epidemiology/Genetics

Hypertrophic cardiomyopathy, an autosomal dominantly inherited condition with a prevalence of 0.2% (1:500) in the general population is the most common cause of sudden cardiac death in young athletes. It presents in all age groups from infancy to the very elderly. There are about 1,500 identified mutations in almost 11 genes encoding the contractile component of sarcomeres. 70% of these mutations belong to the β -myosin heavy chain and myosin-binding protein C (MYBPC). Recent literature has suggested that a mutation in *MYBPC3* is associated with cardiomyopathy and heart failure in South Asian populations. This 25-bp deletion mutation has been found in 4% of individuals in the Indian subcontinent with higher prevalence reported from western and southern India. Lately an emerging subgroup has been identified known as *genotype-positive phenotype-negative* group.

Pathophysiology

The most characteristic abnormality is left ventricular hypertrophy (LVH) with a preserved or smaller left ventricular cavity. The most common form of HCM is asymmetrical septal hypertrophy followed by symmetric, apical and lateral wall hypertrophy. Histopathologically, HCM is characterized by myocardial disarray, myocardial scarring and abnormalities of small intramural coronary arteries. Left ventricular outflow tract (LVOT) obstruction, LV diastolic dysfunction, mitral valve abnormalities, myocardial ischemia and arrhythmias are important pathophysiological abnormalities responsible for various clinical presentations. LVOT obstruction is of a dynamic variety and occurs primarily

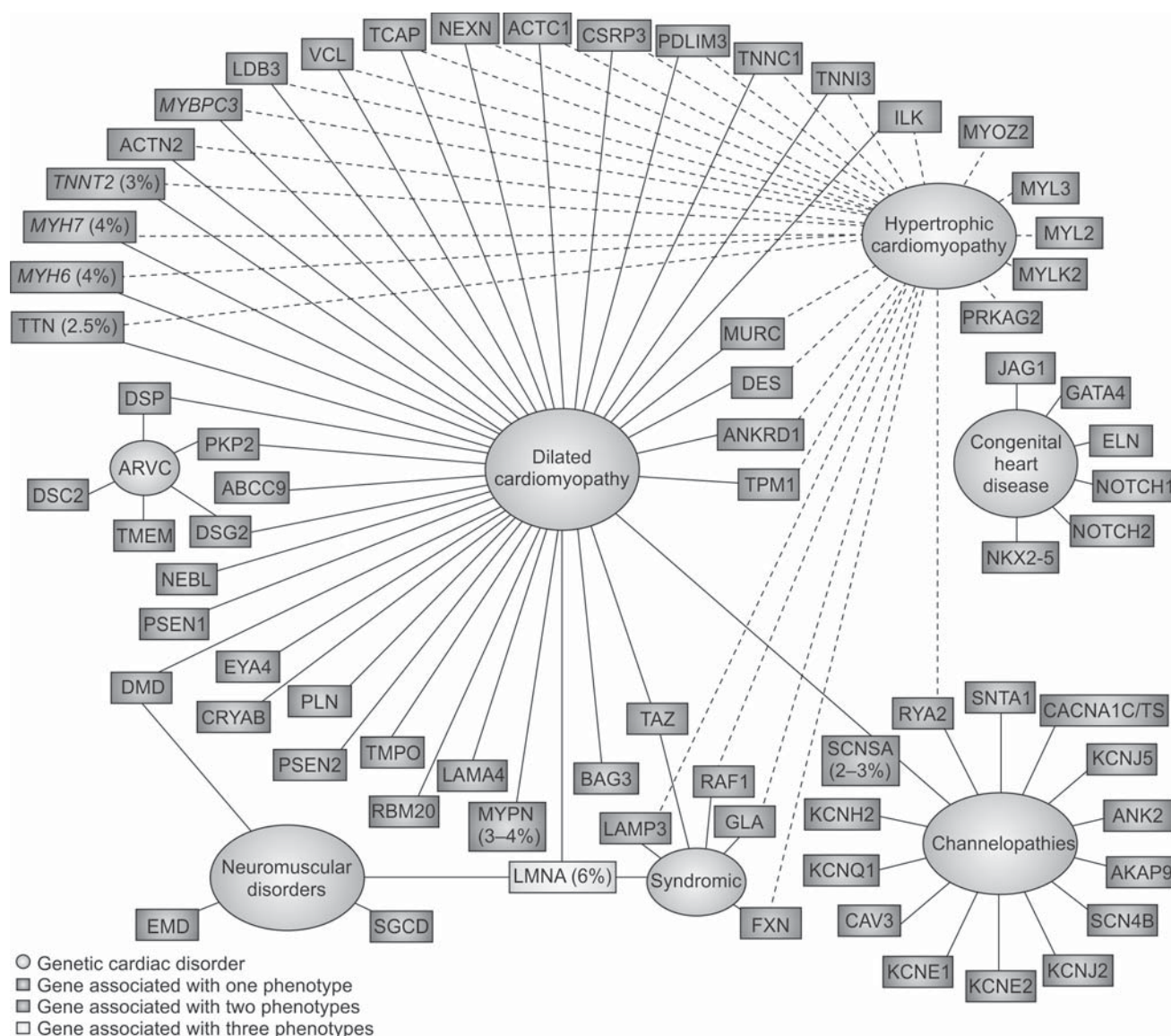


Figure 1 Various genetic mutations causing familial cardiomyopathy. The genetic architecture underlying selected genetic cardiac disorders is shown. Edges (lines) connect each phenotype to the genes that have been implicated in the etiology. Gene nodes associated with familial dilated cardiomyopathy are darker and have bold text if they have been found to cause disease in 1% of patients, and include frequency information if they have been found to cause disease in 3% of patients

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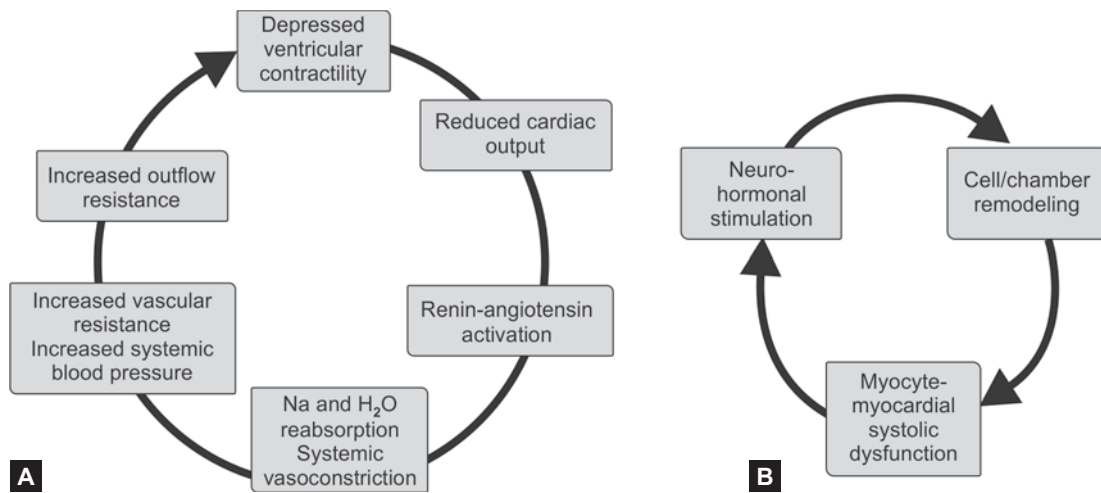
Abbreviation: ARVC, arrhythmogenic right ventricular cardiomyopathy.

from systolic anterior motion (SAM) of mitral valve and subaortic muscular hypertrophy. This obstruction is dynamic being exacerbated by reducing LV volume, lowering systemic vascular resistance and use of positive inotropic agents and improving with increasing LV volume, increasing systemic vascular resistance and use of negative inotropic agents. LV diastolic function is affected earlier than systolic function, often preserved till late. With sustained impaired diastolic function, left atrial enlargement and pulmonary venous congestion leading to congestive symptoms occur. Regional myocardial ischemia commonly occurs in HCM. This could be secondary to either increased capillary density compared to greatly increased muscle mass or small vessel disease with narrowed intramural coronary arteries. Myocardial bridge is noted in 30% of HCM which could also be the etiology of the myocardial ischemia. Right ventricular outflow tract (RVOT)

obstruction from muscle hypertrophy is not uncommon in infants and children; its infrequency in adults suggests its regression with growth.

Clinical Features

Exercise limitation is the predominant symptom in HCM. Others are dyspnea, palpitations, dizziness, chest pain or syncope. Family history is positive in 30–60% of cases. Symptomatic patients show peripheral pulses with sharp upstroke with prominent heaving LV apical thrust. The typical *late peaking* medium pitched, grade 2–3/6 systolic murmur of LVOT obstruction is heard best at mid or lower left sternal border. The murmur gets harsher with the Valsalva maneuver. The murmur of mitral insufficiency is a soft, blowing holosystolic murmur best heard at apex.



Figures 2A and B (A) Pathophysiology; and (B) Neurohumoral adaptation and its interaction with cardiac function and remodeling

Table 3 Clinical presentations of dilated cardiomyopathy

History	
<ul style="list-style-type: none"> Common presenting symptoms – Exercise intolerance – Shortness of breath – Fatigue – Syncope, near syncope – Palpitation – Loss of appetite – Feeding intolerance, poor weight gain and irritability in infants 	<ul style="list-style-type: none"> Less common presenting symptoms – Chest pain – Abdominal pain – Orthopnea – Wheezing – Chronic cough – Frothy sputum
Physical examination	
<ul style="list-style-type: none"> Systemic findings – Respiratory distress, tachypnea – Weak peripheral pulses – Low blood pressure with narrow pulse pressure – Cool extremities – Pitting edema – Hepatomegaly – Increased JVP in older children – Rales and wheezing 	<ul style="list-style-type: none"> Cardiac findings – Tachycardia – Active precordium – Displaced point of maximum impulse – Gallop rhythm – Accentuated P2 (with pulmonary hypertension) – Holosystolic murmur from mitral regurgitation

Abbreviation: JVP, jugular venous pressure.

Diagnosis

Electrocardiography (ECG) features are LVH with ST-T segment changes, deep and narrow Q waves (septal hypertrophy) in left precordial leads. Premature ventricular contractions or various degrees of heart blocks may be seen. T wave inversion in lateral leads is common in cases of apical HCM. ECG in Pompe disease may have a short PR interval. An ECG and a 24-hour Holter monitor are recommended in patients with HCM at baseline and when they become symptomatic.

Echocardiography is diagnostic in HCM, for localizing hypertrophy (LV wall 15 mm or greater in adults and $Z \geq 2$ in children) and quantifying degree of LVOT obstruction. **Figure 4** shows significant septal HCM. Peak LVOT pressure gradient of ≥ 30 mm Hg is considered as obstructive HCM. Systolic anterior motion of SAM mitral valve though commonly seen in obstructive variety however, is not specific for HCM. Left atrial dilatation and abnormal LV filling pattern indicates LV diastolic dysfunction. Systolic function of the LV is usually preserved. Characteristic *spade* deformity on echocardiographic imaging is typical of apical HCM.

Table 4 The diagnostic investigative work-up of dilated cardiomyopathy (DCM) and their findings

Chest X-ray	
Cardiomegaly, increased pulmonary vascular markings and pleural effusion (rarely)	
ECG	
Most common features	Less common features
<ul style="list-style-type: none"> Sinus tachycardia ST-T wave changes Left ventricular hypertrophy 	<ul style="list-style-type: none"> Atrial enlargements Arrhythmias (advanced cases)
Presence of deep Q waves in lead I and a VL in ALCAPA (anomalous left coronary artery from pulmonary artery) presenting as DCM	
Echocardiography	
LV: Marked enlargement with poor contractility (Figure 3) Diastolic dysfunction Mitral valve insufficiency (MV dysfunction)	Look for: Presence of pulmonary hypertension Origin and course of coronary arteries (ALCAPA)
Other tests	
Cardiac catheterization	Useful to document coronary anatomy and obtain endomyocardial biopsy
Biochemical profile	
CBC, CPK, cardiac troponin, CMP, brain natriuretic peptide (BNP) and N-terminal prohormone BNP	Helpful in risk stratification. A BNP level > 300 pg/mL was a strong predictor of death, transplantation, or heart failure hospitalization in a series of pediatric patients
Metabolic work-up	
Urine for organic and amino acids, plasma amino acids, serum lactate, and carnitine and acylcarnitine profile	
Endomyocardial biopsy	

Abbreviations: CBC, complete blood count; CPK, creatine phosphokinase.

Cardiac magnetic resonance imaging is indicated when echocardiography is inconclusive.

Cardiac catheterization though useful in assessing arrhythmia risks, obtaining endocardial biopsy and for pretransplant

Table 5 Prognosis and indicators of survival in childhood dilated cardiomyopathy (DCM)

Prognostic predictors of survival in DCM	
Poor survival	Improved survival
<ul style="list-style-type: none"> • Familial cardiomyopathy • Markedly elevated ventricular end-diastolic pressures • Presence of ventricular arrhythmias • Persistent heart failure • Tissue diagnosis of endocardial fibroelastosis coexistence of right ventricular dysfunction 	<ul style="list-style-type: none"> • Treatable causes of DCM with early detection and appropriate treatment • Improved shortening fraction over 1–6 months after presentation • Tissue diagnosis of myocarditis • Younger age

evaluation is not required for diagnostic purposes in current practice.

Genetic testing may be positive in 60–70% of patients with HCM. Genetic testing to identify mutations is recommended in a proband with HCM, atypical clinical presentation and suspected genetic condition. Patients who undergo genetic testing should also receive genetic counseling by a genetic specialist. Screening with or without genetic testing is recommended in all first degree relatives of a patient with HCM.

Sports Participation

Current practice includes at least personal history, family history and physical examination before sports participation. In the United States, use of 12 lead ECG is not included routinely in

screening process. In the presence of a positive family history of HCM or sudden death or positive genetic mutation, further testing should be considered. It may be challenging to differentiate benign physiologic hypertrophy of the athlete's heart from HCM. An athlete's heart has LV wall thickness usually 13 mm or less, LV dimensions larger than 55 mm, normal LV filling pattern and maximum oxygen consumption of more than 45 mL/kg/min (> 110% predicted) on stress test.

It is reasonable for a patient with HCM to participate in low intensity competitive sports or recreational sports. Participation in intense competitive sports is prohibited regardless of age, sex, race, presence or absence of LVOT obstruction, prior therapies for HCM or implantable cardioverter defibrillator (ICD) because of the high-risk of cardiac arrest.

Management

In symptomatic patients, management objectives of HCM are:

- To reduce ventricular contractility
- To improve ventricular compliance
- To increase ventricular volume.

Beta-blockers are the first-line agents followed by calcium channels blockers (verapamil) in those patients who are unable to tolerate beta-blockers or those with symptoms uncontrolled by beta-blockers alone. Beta-blockers improve the symptoms by negative chronotropic and inotropic effect. *Disopyramide* can be added in patients who do not respond to the earlier therapy. Propranolol is preferred for infants and children while atenolol is preferred for adolescents.

Table 6 Drug treatment of dilated cardiomyopathy in children

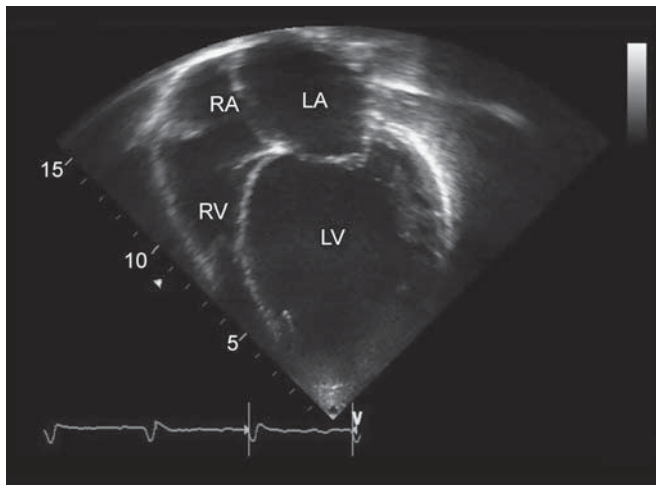
Agent/Drug	Comments
<i>Combined vasodilator and inotropic agents</i>	
Milrinone (PDEI)	Preferred in the hospitalized patients because of its ability to increase stroke work and thus cardiac output, decrease systemic and pulmonary vascular resistance and its unique lusitropic properties; Synergistic effects of milrinone with catecholamines may be beneficial
Levosimendan (PDEI)	Oral agent with similar properties as milrinone; no superiority over dobutamine
<i>Catecholamines</i>	
Dopamine, dobutamine	Frequently used; need for extreme caution in use: Arrhythmogenic properties and pronounced α -adrenergic effect if the patient is on β -blocker therapy
<i>Cardiac glycosides</i>	
Digoxin	Widely used in a long-term management of DCM; Improves LV contractility; not recommended in asymptomatic children with LV dysfunction; cautious use in acute HF (induces arrhythmia in inflamed myocardium; and increased toxicity in renal impairment)
<i>Diuretics: Mainstay of supportive therapy</i>	
Furosemide	Agent of choice; often, combined with weak diuretics like spironolactone to avoid hypokalemia and improve diuresis
Spironolactone	Independently shown to improve survival in patients with heart failure and should be included in long-term management
<i>Vasodilator agents: Used to decrease afterload and improve cardiac output</i>	
Nitroprusside Hydralazine	Used in acute settings
<i>ACE inhibitors: First choice for long-term use</i>	
Enalapril	Improved survival in chronic HF (multicenter study)
Angiotensin receptor blocker (ARBs)	Tried if ACEi is not tolerated due to distressing cough
<i>Beta-blockers</i>	
Carvedilol	Improves LV performance and clinical status in adults; in children, no such beneficial effect seen (RPCMCT). Despite this, beta-blockers have remained widely used in CHF

Abbreviations: PDEI, phosphodiesterase inhibitor; HF, heart failure; ACE, angiotensin converting enzyme; RPCMCT, randomized, placebo controlled multicenter trial.

Table 7 Other therapeutic modalities employed in the management of dilated cardiomyopathy (DCM)

<i>Salt and water restrictions</i>	
<i>Antithrombotic therapy:</i> Prevention and treatment of thrombus	
Antiplatelet therapy (aspirin)	Should be initiated, given the propensity for developing thrombus
Warfarin (long-term)	Aggressive treatment of thrombi if found, initially with aspirin
<i>Antiarrhythmic therapy:</i> Prevention and treatment of life-threatening arrhythmias	
Amiodarone	Used safely in children
Procainamide	To be used cautiously because of its negative inotropic effects
<i>Immunosuppressive agents:</i> Its role in DCM immunologically mediated or inflammatory myocarditis is still unproven	
Steroids, cyclosporine and azathioprine	Utility unproved in studies
Carnitine supplements	Provided, if deficiency detected
Growth hormone	Improved LV ejection fraction (in several uncontrolled studies)
<i>Mechanical circulatory supports</i>	
ECMO or VAD	May be required in acute settings or as a bridge to transplantation
Heart transplantation	Consider those children with DCM who are refractory to medical therapy, VAD dependent or requiring frequent inotropic support and whose likelihood of short-term survival is unfavorable
<i>Prevention of sudden cardiac death (SCD):</i> SCD incidence is about 1% of children with DCM	
Use of ICDs	May not be justified for primary prevention; well accepted for secondary prevention
Cardiac resynchronization	Needs further evaluation in pediatric population

Abbreviations: ICD, implantable cardioverter defibrillator; ECMO, extracorporeal membrane oxygenation; VAD, ventricular assist device.

**Figure 3** Four-chamber view of echocardiogram in dilated cardiomyopathy (DCM) its interaction with cardiac function and remodeling

Calcium channel blockers should be avoided in children less than 1 year of age. Specific antiarrhythmic medications should be used for documented arrhythmias. Anticoagulation and ventricular rate control medications are indicated in patients with paroxysmal, persistent or chronic atrial fibrillation with HCM.

Inotropic agents and vasodilators are contraindicated in obstructive HCM. In acute hypotension, pure vasoconstrictors such as phenylephrine should be used. Diuretics are generally avoided because they can be harmful by depleting LV volume however, in severe secondary heart failure, they can be used judiciously to relieve congestive symptoms.

Surgical myomectomy should be considered in a symptomatic children with LVOT gradient of more than 50 mm Hg and failed medical management.

Other forms of therapies such as *alcohol septal ablation*, *dual chamber pacemaker* or *mitral valve replacement* have not been routinely performed in children with HCM. Consideration for *heart transplantation* may be required in certain selected cases such as refractory arrhythmia or children with HCM and restrictive physiology and advanced heart failure that are not responsive to other therapeutic interventions.

Medical management can offer symptomatic relief; however it cannot reduce the risk of sudden death or heart failure. ICDs have been shown to reduce the incidence of sudden cardiac death (SCD).

Risk factors for sudden death includes prior history of ventricular tachycardia, ventricular fibrillation or aborted SCD, unexplained syncope LV thickness of more than or equal to 30 mm, abnormal blood pressure response during exercise (failure to rise by at least 20 mm Hg or a drop of at least 20 mm Hg at peak exercise) and family history of SCD. All patients with HCM should undergo comprehensive SCD risk stratification in order to determine the need for ICD placement.

Affected individuals should be restricted from moderate to high intensity competitive sports. Comorbidities like hypertension, diabetes, hyperlipidemia or obesity should be treated.

Follow-up Visits

Frequent follow ups with ECG, echocardiogram and/or a 24-hour Holter monitor (12–18 months in children and adolescents) are required for asymptomatic children to monitor for LVOT obstruction, presence of arrhythmia and degree of progression of hypertrophy.

Prognosis

Hypertrophic cardiomyopathy with a diverse clinical presentation and course has annual mortality rate which is slightly higher in children compared to adults (2% vs. 1% per year). Most patients with HCM may also have normal life expectancy. Difficulty in predicting outcome in children with HCM is inherent for such a heterogeneous disease over long periods.

Several other conditions manifest with LVH and mimic typical HCM caused by sarcomere protein mutations as described in **Table 8**. Long-term prognosis in the infant with HCM and metabolic disease is poor.

RESTRICTIVE CARDIOMYOPATHY

Restrictive cardiomyopathy (RCM) is a rare form of chronic heart disease characterized by normal or decreased volume of both ventricles associated with biatrial enlargement, normal left ventricular wall thickness and AV valves, impaired ventricular filling with restrictive physiology and normal (or near normal) systolic function.

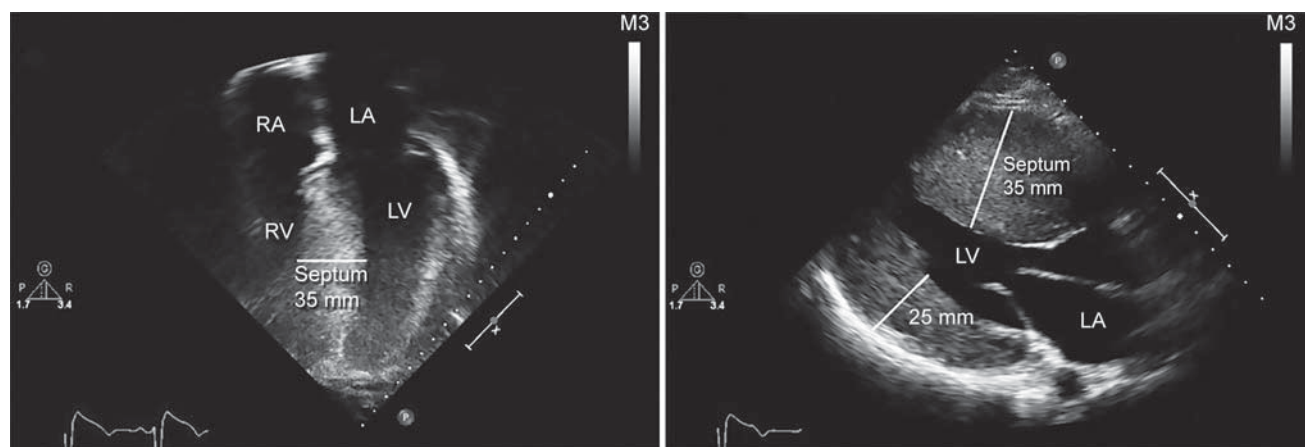


Figure 4 Echocardiography of hypertrophic cardiomyopathy

Table 8 Inherited form of hypertrophic cardiomyopathy (HCM) from nonsarcoplasmic mutations

Conditions	Gene/enzyme	Inheritance	Clinical features	Prognosis
Noonan syndrome	<i>PTPN11</i> mutation	Autosomal dominant	LV hypertrophy, dysplastic pulmonary valve stenosis and atrial septal defect	Good
Fabry disease	α -galactosidase A deficiency	X-linked recessive	Angiokeratomas, corneal clouding, peripheral neuropathy, renal failure, anhydrosis	Poor unless treated with enzyme replacement therapy
Pompe disease	α -1,4 glucosidase deficiency	Autosomal recessive	HCM, hypotonia, hepatomegaly, ECG: short PR interval, biventricular hypertrophy	Death before 2 years unless received enzyme therapy
Danon disease	<i>LAMP2</i> gene mutation	X-linked semi-dominant	Cardiomyopathy, intellectual disability, skeletal muscle weakness	Poor
Others	<i>PRKAG2</i> mutation	Autosomal dominant	Progressive LVH, conduction system abnormalities, proximal myopathy	Poor

Abbreviation: LVH, left ventricular hypertrophy.

Epidemiology and Genetics

Restrictive cardiomyopathy in children represents 2.5–5% of all diagnosed cardiomyopathies. In children, the average age of diagnosis is 6 years. The frequency of RCM in both sexes is similar. The family history is positive in 30% of children. At least 10 genetic mutations have been found to be associated with RCM phenotype. Sarcomeric protein mutations have been described in troponin I, troponin T, α -cardiac actin, MYBPC and β -myosin heavy chain. Nonsarcomeric mutations in genes coding for proteins such as like desmin, RSK2 (Coffin-Lowry syndrome), lamin A/C (Emery-Dreifuss) and transthyretin have been described.

Etiology

Restrictive cardiomyopathy can be caused by multiple etiologies as given in **Table 9**. In tropical countries, endomyocardial fibrosis (EMF) is considered to be the most common cause of RCM. Outside of the tropics, idiopathic RCM is the most common cause, followed by anthracycline toxicity.

Pathophysiology

In RCM, ventricular chamber dimensions, wall thickness and systolic function are usually preserved. Most ventricular filling occurs in rapid filling phase with little or no filling in late diastole. Because of the stiff ventricular walls, ventricular filling pressures are increased, leading to marked atrial dilation. This ultimately leads to pulmonary and/or systemic venous congestion. Coronary ischemia may also be encountered in this population. A possible mechanism of ischemia could be diffuse hypoperfusion of the

subendocardial myocardium from impaired coronary perfusion secondary to high ventricular filling pressure rather than coronary anomalies per se.

Clinical Features

Children with RCM usually present with respiratory symptoms. With left ventricular involvement, cough, dyspnea, chest pain, exercise intolerance or syncope may occur. Syncope occurs in about 10% of this population and could be secondary to thromboembolism, ischemia or arrhythmias. With right ventricular involvement, lower limb edema, hepatomegaly and ascites may occur.

Physical examination may reveal jugular venous distension, loud P_2 (from pulmonary hypertension) and systolic murmur from AV valve insufficiency. Crackles in lungs, hepatomegaly, ascites, and edema are also common findings in advanced disease.

Diagnosis

Chest X-ray is usually positive for cardiomegaly from enlarged atria, pulmonary venous congestion and occasionally pleural effusion.

ECG demonstrates typical left and right atrial enlargements with peaked P waves. ST-T wave changes and ST segment depression is seen frequently. Arrhythmias/conduction disturbances have been found in 15% of pediatric patients with RCM and therefore, a 24-hour Holter monitor is recommended to diagnose occult arrhythmia.

Echocardiography is the corner stone of diagnosis. Marked atrial dilation is easily identifiable. Ventricular systolic function is usually preserved; however, in severe cases LV dysfunction may be

Table 9 Etiology of restrictive cardiomyopathy

Idiopathic
Familial/genetic
Storage disorders—Hurler syndrome, Gaucher disease, Fabry disease, glycogen storage diseases
Endomyocardial—endomyocardial fibrosis, hypereosinophilia syndrome (HES), endomyocardial fibroelastosis, carcinoid
Infiltrative disorders—hemochromatosis, amyloidosis, sarcoidosis, cystinosis, fatty infiltration, metastatic cancers
Myocarditis
Radiation
Post-heart transplant
Drugs—anthracycline, serotonin, methysergide, ergotamine
Scleroderma
Genetic syndromes—Emery-Dreifuss syndrome, Coffin-Lowry syndrome

present. Although ventricular wall dimensions are normal in the majority of the cases, it is not unusual to find various degrees of hypertrophy. This may be true particularly for the subset of patients with troponin I mutation. In EMF, AV valves can also be involved, leading to thickened valve leaflets and decreased excursions. The presence of thrombus and pulmonary hypertension should always be looked for. Pericardial thickening may direct the diagnosis towards constrictive pericarditis rather than RCM. Abnormal Doppler indices suggest LV diastolic dysfunction.

Cardiac catheterization is indicated at the time of the diagnosis to document detailed hemodynamics. A classic early diastolic dip followed by a plateau pattern known as a *square root sign* is noted on catheterization. Cardiac catheterization is also helpful in differentiating RCM from constrictive pericarditis (CP) which is a readily treatable disease.

Management

The therapy is mostly supportive and directed towards relieving symptoms. Diuretics though helpful in abating congestive symptoms must be carefully used; over-diuresis is avoided because of the sensitivity of these patients to preload. Antiplatelet and/or anticoagulation therapies should be considered for all patients. ACE inhibitors reduce systemic vascular resistance without increasing cardiac output in RCM and thus are not beneficial. The role of beta-blockers in children with RCM has not been studied. Arrhythmias should be treated accordingly. Some children may require a pacemaker for complete heart block. Pulmonary hypertension eventually occurs in all patients. It is treated with oral or IV pulmonary vasodilators. Cardiac transplantation is the only definitive therapy currently available. Early transplantation is preferable before pulmonary hypertension ensues.

Prognosis

The prognosis of RCM is generally poor with an annual mortality rate of 7%. The 2-year mortality rate is as high as 50%. Sudden death has been reported from 14% to 33% in children with RCM. Poor prognostic factors have not been well-defined in children.

OTHER CARDIOMYOPATHIES

Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia

Arrhythmogenic right ventricular cardiomyopathy (ARVC), often inherited as an autosomal dominant cardiomyopathy,

is characterized by right ventricular (RV) myocyte loss with fibrofatty replacement that predisposes the child to increased risk of ventricular arrhythmias and sudden death. It is more common in Europe, especially Italy. Mutations in desmoplakin (DSP), *plakophilin-2*, and *desmoglein-2* and *desmocollin-2* genes are observed. Naxos disease with mutations in plakoglobin (palmoplantar keratoderma and woolly hair) and Carvajal syndrome (mutation in desmoplakin,) are two recessive forms with this type of cardiomyopathy. Possible infection/inflammatory process by coxsackievirus B13 and adenovirus have been implicated. Fatty and fibrofatty replacement of the RV myocardium leads to thinning of the wall, aneurysms, RV dilatation and regional/global RV dysfunction. Involvement of LV may also occur. The essential details are given in the **Table 10**.

Left Ventricular Noncompaction

Left ventricular noncompaction (LVNC), described as a primary genetic cardiomyopathy due to mutations on at least nine different genes, is characterized by an abnormal (spongy) myocardium with prominent trabeculae and deep intertrabecular recesses communicating with the LV cavity and resulting into two distinct layers comprising compacted and noncompacted myocardium. A maturational arrest in the process of normal compaction during fetal life is the postulated mechanism. Sporadic cases have also been reported. The disease is progressive with worsening of LV function, arrhythmias and thromboembolic complications. Treatment is directed towards anticongestive measures, antiarrhythmic therapy and antiplatelet or anticoagulation therapy. Cardiac transplantation may also be considered in selected patients who are refractory to medical therapy. The essential details are given in the **Table 11**.

Asymmetric Septal Hypertrophy in Infants of a Diabetic Mother

Asymmetric hypertrophy with pronounced septal involvement compared to the ventricular free walls is more commonly observed in infants of a diabetic mother (IDMs) besides other congenital heart defects. The overall incidence of LV hypertrophy is 10–20%. Hyperinsulinemia leads to the ventricular hypertrophy during fetal life. This is a special group with the highest incidence of regression of LV hypertrophy. These infants are macrosomic, plethoric and may have tachypnea and/or tachycardia. Congestive heart failure may develop in 5–10% of affected infants. Echocardiogram shows LVH with or without obstruction. Beta-blockers are the mainstay of treatment in the obstructive variety. In severe heart failure, pure alpha agonists such as phenylephrine should be used to maintain blood pressure. Typically, ventricular hypertrophy regresses within the first few months of life.

Cardiomyopathy in Duchenne Muscular Dystrophy

Duchenne muscular dystrophy (DMD), transmitted in X-linked recessive fashion, is caused by the defect of the dystrophin gene leading to absence of dystrophin. Dystrophin is present in skeletal muscles, cardiac muscles, neurons and smooth muscles. It is the most common muscular dystrophy in children with an incidence of 30 per 100,000 livebirths. Absence of dystrophin makes cell membrane vulnerable to injury resulting into endomysial fibrosis. Skeletal muscles are primarily affected leading to respiratory compromise.

Cardiomyopathy is invariably associated with DMD. In advanced cases, symptoms of heart failure such as dyspnea, orthopnea and edema may occur. Symptoms are often inseparable from the respiratory dysfunction. The earliest sign of affected cardiac function is unexplained tachycardia that does not change

Table 10 Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC)

Estimated prevalence	1 per 5,000
Usual age of onset of symptoms	20 years of age and beyond
Clinical features	Palpitations, syncope, arrhythmias—ventricular tachycardia (VT), sudden cardiac death (SCD)
Diagnosis*	
ECG	Epsilon waves (undulation in the ST segment indicative of postexcitation low amplitude potential), T wave inversion in V1-V3 (important between ages 19 and 45) and prolonged S wave stroke. Left bundle branch morphology is more common and seen with tachycardia
Echocardiography	Enlarged and thin RV with decreased regional/global systolic performance
MRI (diagnostic)	Global and regional ventricular dilation, global and regional ventricular dysfunction, intramyocardial fat, focal wall thinning and late gadolinium enhancement
Cardiac catheterization	Resorted to: (1) to obtain hemodynamic information, and (2) to obtain endocardial biopsy
Management	
To prevent sudden cardiac death	Implantation of ICD: Warranted as primary preventive measure in high-risk patients. Definitely indicated for secondary prevention
To decrease the frequency of sustained VT episodes	Catheter ablation
To reduce the frequency of arrhythmia	Beta-blockers—its use, however, may not reduce the risk of sudden cardiac death

Abbreviation: MRI, magnetic resonance imaging.

*Diagnostic criteria have been published recently and reference can be found in the *More on this topic*.

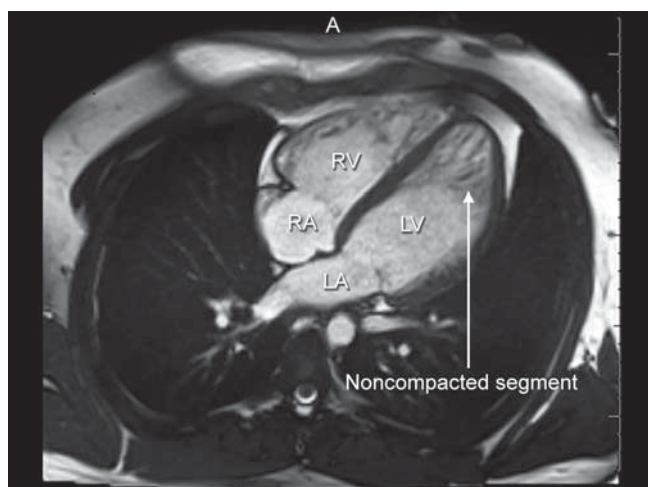
Table 11 Left ventricular noncompaction (LVNC)

Onset of symptoms	Only at late age
Primary symptoms and signs	Symptoms of heart failure
Other findings	Neurological disorders in about one-third
Differential diagnosis	Metabolic myocardial diseases especially mitochondrial disorders and Barth syndrome (<i>Tafazzin</i> gene mutation) must be excluded
Diagnostic investigations	
ECG	Giant QRS complexes, T wave changes and WPW pattern
Echocardiography	Diagnostic; thin compacted and thick noncompacted regions of the myocardium with visible trabeculations. LV involvement can be segmental involving predominantly apical segment of LV or global; ratio of compacted to total (noncompacted + compacted myocardium) during diastole less than 0.5 is diagnostic
Cardiac MRI (Figure 5)	Considered when echocardiography is inconclusive; ratio of noncompacted to compacted myocardium more than 2.3 is diagnostic

Abbreviation: MRI, magnetic resonance imaging.

with increasing age. This is thought to be from an increased sympathetic response to ventricular dysfunction. ECG may also demonstrate pathologic Q representing myocardial scarring or infarct. Other conduction abnormalities such bundle branch block and heart block may be present secondary to involvement of Purkinje system. Fatal ventricular arrhythmias can occur in severe ventricular dysfunction.

Echocardiography demonstrates inappropriately reduced LV wall thickness and increased LV dimensions. Ventricular systolic function is affected first and commonly present after 10 years of age. The degree of ventricular systolic dysfunction and skeletal muscle dysfunction do not correlate. No specific treatment is

**Figure 5** Cardiac magnetic resonance (CMR) of left ventricular noncompaction (4-chamber view)

available to halt the progression of cardiac dysfunction. Treatment is directed towards relieving heart failure symptoms. Therapies aimed at decreasing fibrosis such as immunosuppressants including steroids have been shown to improve muscle strength in DMD. Care should be taken in subjecting these patients to any type of surgery as anesthetic complications such as hyperthermia, cardiac arrest or rhabdomyolysis are more prone to occur in the presence of cardiac dysfunction. In high-risk patients with severe ventricular dysfunction, only emergent surgical procedures should be undertaken. DMD patients have an average survival of 20 years or less, with respiratory compromise being the primary reason for death.

Anthracycline Induced Cardiomyopathy

Doxorubicin (anthracycline), used as chemotherapeutic agents in several childhood cancers, has been shown to affect heart function due to its ability to generate reactive oxygen species causing lipid

peroxidation of the myocyte cell membrane and subsequent cell injury. Anthracycline induced cardiomyopathy exhibits in different phases: acute phase—symptoms within 1 week of treatment, occurs very rarely; early-onset—symptoms occurring within 1 year; and late-onset—symptoms occurring after 1 year. Clinical heart failure, decreased exercise capacity and arrhythmias are common. Clinical congestive heart failure correlates with total cumulative dose. Although there is no safe dose of doxorubicin, a total cumulative dose of less than 300 mg/m² is hardly associated with significant adverse effect on LV contractility. Symptomatic heart failure is seen in 2–5% of patients at doses of 400–500 mg/m². Elevated cardiac troponin-T and N-terminal pro-brain natriuretic peptide within 90 days of treatment were associated with abnormal LV structure and function at 4 years after diagnosis may suggest their usefulness in monitoring disease progression.

Modifiable risk factors include obesity, dyslipidemia, metabolic syndrome, type-2 diabetes, mediastinal radiation, total cumulative dose, hypertension, and treatment with cyclophosphamide, paclitaxel, or trastuzumab. **Nonmodifiable risk factors** include younger age (especially < 4 years), female gender, trisomy 21, African-American ethnicity, and genetic mutation of the *HFE* gene associated with hereditary hemochromatosis.

Prevention

Limiting the total cumulative dose to less than 300 mg/m² has been suggested. Structurally modified anthracyclines such as epirubicin or idarubicin and liposomal derivatives of anthracycline to reduce cardiotoxicity can be tried. Cardioprotection from agents that reduces production of free oxygen radicals such as dexrazoxane has brought promising results. Other antioxidants such as N-acetyl cysteine, vitamin E, L-carnitine and coenzyme-Q have been tried with variable success. Carvedilol also has mild antioxidant effect besides being a beta-blocker. Amifostine, a selective cardioprotector, as demonstrated in rat studies, does not interfere with the antineoplastic action of anthracyclines.

Treatment

The general consensus is to discontinue anthracycline therapy with the onset of clinical heart failure. ACE inhibitors and beta-blockers have been shown to be of benefit in halting the progress of LV dysfunction in idiopathic cardiomyopathy; however, their benefit is unproven in anthracycline-induced cardiomyopathy. Growth hormone therapy is still in experimental phases with potential of short-term benefit.

Prognosis

It is generally poor if clinical heart failure sets in. Cardiac transplantation may be beneficial in the long-term if probability of tumor recurrence is low.

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IN A NUTSHELL

1. Myocardial diseases, inherited or acquired, constitute a major cause of cardiovascular morbidity and mortality in children.
2. Myocarditis is an inflammatory disease of the myocardium and the most common known cause of dilated cardiomyopathy in children.
3. Dilated cardiomyopathy is the most common form of cardiomyopathy in children which is characterized by the ventricular dilation and systolic dysfunction resulting into congestive heart failure.
4. Hypertrophic cardiomyopathy, a genetically inherited disease, is associated with ventricular hypertrophy and represents the most common cause of sudden death in adolescents and young adults.
5. Restrictive cardiomyopathy is a rare cardiomyopathy and has poor prognosis.
6. Treatment includes management of heart failure symptoms and prevention of arrhythmia, thromboembolic complications and sudden death.
7. Heart transplantation is the therapy of choice for end-stage cardiomyopathies refractory to medical therapy.

Chapter 40.36

Diseases of the Pericardium

Manoj Kumar Rohit, Ankur Gupta

Pericardium, a double layered structure consists of inner serosal visceral pericardium adhering to the myocardium and an outer fibrous parietal pericardium consisting of elastic fibers and collagen. About 30 mL of pericardial fluid in this space lubricates the heart during its contraction. Its blood supply is from the internal mammary arteries and the descending aorta. It is innervated by the vagus, phrenic and sympathetic fibers.

ETIOLOGY

The causes of pericardial diseases are (**Table 1**):

- Infectious,
- Noninfectious, and
- Congenital.

Table 1 Causes of pericarditis and pericardial diseases in children

Infectious	
Viral	Echovirus, coxsackievirus, adenovirus, influenza, cytomegalovirus
Bacterial	<i>Haemophilus influenzae</i> , <i>Streptococcus</i> , <i>Staphylococcus</i> , gram-negative organisms
Mycobacterial	<i>Mycobacterium tuberculosis</i> , <i>Mycobacterium avium-intracellulare</i>
Fungal	<i>Histoplasma</i> , <i>Candida albicans</i>
Protozoal	<i>Toxoplasma</i> , <i>Echinococcus</i>
Noninfectious	
Connective tissue disorders	Acute rheumatic fever, rheumatoid arthritis, systemic lupus erythematosus, mixed connective tissue disorders, systemic sclerosis
Metabolic	Nephrogenic, hypothyroidism, Gaucher disease
Traumatic	Surgery, blunt and penetrating trauma
Neoplastic	Primary and secondary (leukemia, lymphoma)
Congenital	
Cysts, absence of pericardium, Mulibrey nanism	

ACUTE PERICARDITIS

Clinical Features

Acute pericarditis is a syndrome characterized by chest pain, pericardial friction rub and electrocardiographic changes. Child gives history of retrosternal pain often radiating to the trapezius ridge and which increases on lying down and in inspiration and decreases with sitting posture. Pericardial friction rub has a superficial, scratchy character and may be heard anywhere over the precordium. A monophasic rub is confined to ventricular systole, biphasic includes atrial systole and triphasic rub includes ventricular diastolic filling.

Electrocardiographic Changes

The PR, ST-T wave changes in the electrocardiograph (ECG) are diffuse and may confirm the clinical suspicion of pericarditis. Characteristics findings on the ECG include PR depression in all the leads except aVR and ST elevations (concave upwards and < 5 mm elevation; **Figure 1**) which is followed by the settling of the ST elevations and subsequently T wave inversions with complete normalization of the ECG in a typical 2 weeks period. However, only 50% patients display all ECG changes. Close differential diagnosis are acute myocardial infarction and early repolarization variant. Unlike adult myocardial infarction does not occur in young children except in case of *anomalous origin of left coronary from pulmonary artery* which has typically lateral wall infarct (Q waves with T wave inversion in lead I, aVL and V4-V6 on ECG) and picture of significant left ventricular systolic dysfunction.

Diagnosis

The aim of imaging and laboratory studies is to find the etiology of acute pericarditis. It includes chest X-ray, detailed ECG and blood markers of inflammation including erythrocyte sedimentation rate (ESR) and white blood cell count. An extensive evaluation is generally not required in a healthy child in whom pericarditis is preceded by a viral prodrome as such patients have a self-limiting course. Etiological factors like trauma, myocarditis, systemic lupus erythematosus (SLE) and purulent pericarditis should be considered in children if history or any clinical features suggest.

Treatment

Primary treatment is for the underlying etiology. Antibiotics remain the mainstay for bacterial infections. Acute pericarditis of noninfectious origin usually responds to nonsteroidal anti-inflammatory drugs (NSAIDs) like acetylsalicylic acid or ibuprofen.

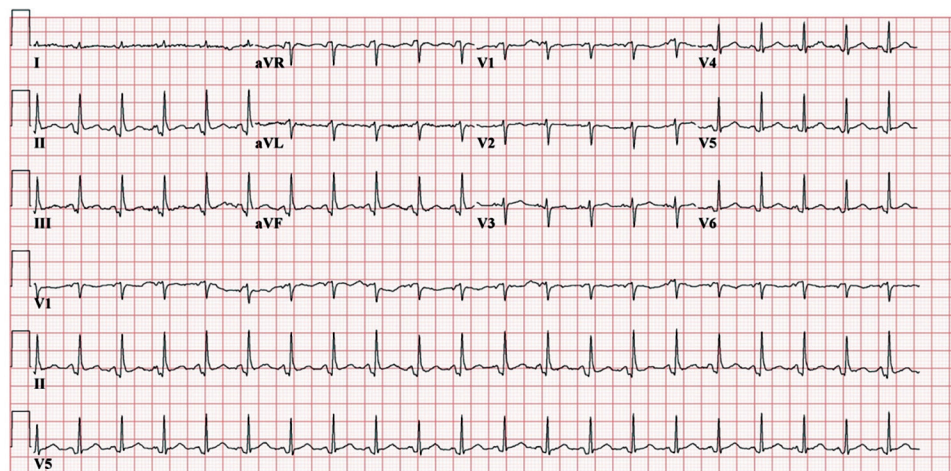


Figure 1 Electrocardiograph (ECG) of a patient with acute pericarditis showing PR depression in all the leads except aVR and diffuse, nonspecific, concave ST segment elevations

In adults, colchicines either as a supplement to NSAIDs or as monotherapy especially in recurrent cases (20–50% patients) is also effective. Experience of colchicines use in children is limited to be recommended for use at this stage. Some cases, particularly of connective tissue disease or uremic pericarditis, may require steroid treatment (prednisolone 1 mg/kg/day) for a week which may be tapered on an individual basis.

SPECIFIC FORMS OF PERICARDITIS

Viral Pericarditis

It is the most common form of pericarditis in children, though more often viral infection is presumed rather than proved. Around 50% children present with viral prodrome, with pericardial friction rub being present in up to 80% patients. Viral isolation from pericardial fluid or viral polymerase chain reaction (PCR) in pericardial fluid or a rise in the viral neutralizing antibodies in the acute and convalescent phase serum is done for a definitive diagnosis. Treatment remains symptomatic with bed rest and NSAIDs. Steroid therapy is rarely indicated.

Bacterial Pericarditis

Etiology and Risk Factors

Bacterial pericarditis is frequently caused by streptococci, staphylococci, and gram-negative organisms with *Haemophilus influenzae* being an important cause in children. *Staphylococcus aureus* is the most common causative agent in our settings. Predisposing factors are immunosuppression, chronic diseases, cardiac surgery and trauma.

Clinical Features

The typical features of pericarditis are usually absent and the course is fulminant with rapid progression to cardiac tamponade. Such patients usually have widespread systemic infection and sepsis and pericarditis is often missed.

Management

Diagnosis is made on echocardiography and purulent effusion should be drained and appropriate antibiotics should be started. Pericardial window should be created for recurrent or nonrelapsing effusions. Pericardiectomy is required for dense adhesions, loculated effusions, recurrent tamponade and in patients who develop constrictive pericarditis. Acute bacterial pericardial effusion generally requires drainage either by surgery or percutaneously along with antibiotics. In centers where facility for cardiac surgery is not available, intrapericardial instillation of streptokinase by dissolving the fibrinous components of the exudates is thought to be helpful.

Outcome

Mortality despite treatment remains high (around 40%).

Tubercular Pericarditis

Tuberculosis remains the most important cause of pericarditis, both in the adults and in children, in India. Its incidence is increasing because of human immunodeficiency virus (HIV) infection. Tubercular pericarditis is a delayed hypersensitivity response to the antigens of the tubercular bacilli which enters the pericardium either directly from the infected mediastinal lymph nodes or through the hematogenous route. Typical symptoms of pericarditis like pain and pericardial friction rub are absent and the child presents with chronic symptoms of fever, decreased appetite, weight loss and night sweats. An acute phase of inflammation progresses finally in constriction in about 50% patients.

Management

Definitive diagnosis of tubercular pericarditis on the basis of histological examination and culture of *Mycobacterium tuberculosis* is difficult. Indirect diagnostic tests like PCR detected *M. tuberculosis* DNA and elevated levels of adenosine deaminase, lysozyme and interferon gamma in pericardial fluid are more helpful in clinical settings. Patients with tubercular pericarditis should be treated with a regimen of isoniazid, rifampicin, pyrazinamide and ethambutol for 2 months and continued on isoniazid and rifampicin for further 4 months. Corticosteroids (prednisolone 1 mg/kg/day) may be given for initial 2 months and benefits by reducing morbidity and mortality, but definitive data regarding lack of progression to constrictive pericarditis is lacking. As around 50% patients develop constrictive pericarditis, they will require pericardiectomy.

Noninfectious Pericarditis

Pericarditis may be present in any connective tissue disorder and presents as acute or chronic pericarditis with or without effusion. Pericardial involvement in acute rheumatic fever is seen in about 10% patients and occurs as a part of pancarditis. It is not associated with increased mortality and is treated with NSAIDs. Symptomatic pericarditis occurs in about 10% children with juvenile rheumatoid arthritis and in 25% children with SLE, though asymptomatic pericardial involvement diagnosed on the basis of echocardiography occurs in up to 50% patients. Treatment is with NSAIDs accompanied with a short course of steroids.

Pericarditis in renal failure is associated with uremia. Patients are usually asymptomatic and may present with large pericardial effusion of even cardiac tamponade. Treatment involves NSAIDs and intensification of dialysis. Cases of resistant or recurrent effusions require drainage or even pericardial window or pericardiectomy.

Pericardial effusion is seen in up to 33% patients with myxedema. The patients are not much symptomatic due to pericarditis and present with bradycardia. The effusion develops slowly and responds to thyroid supplementation. Pericardial tamponade is rare. And hence in cases of idiopathic pericardial effusions besides routine test thyroid stimulating hormone (TSH), antinuclear antibody (ANA) should also be done regularly.

CONGENITAL PERICARDIAL DISEASE

Pericardial Cysts

Pericardial cysts are formed due to defective embryological development of the pericardium. These are usually benign and are incidentally detected in an asymptomatic patient on a chest X-ray. Though they can be present in hilar or mediastinal location but are most commonly found in right costophrenic angle. A computed tomography (CT) chest can be done to help differentiate from a neoplasm. Usually no treatment is required.

Congenital Absence of Pericardium

Congenital absence of the pericardium is a rare anomaly which may involve a part or whole of the pericardium. Left side defects are much more common than the right side. Mostly the patients are asymptomatic and are diagnosed when a chest X-ray reveals leftward displacement of the heart border. Some patients may be symptomatic with chest pain, syncope and even sudden death which may be related to herniation of the left atrial appendage or torsion of the great vessels. Congenital heart and pulmonary anomalies are present in 30% patients. ECG is either normal or shows incomplete right bundle branch block. Echocardiography reveals a dilated right ventricle and paradoxical septal motion. Magnetic resonance imaging (MRI) and CT are confirmative

diagnostic tests. Size of the pericardial defect dictates the need for surgical treatment. Complete absence and very small defects do not need any treatment. The defects in the patients with risk of cardiac herniation are either closed by patch closure or enlarged to prevent incarceration.

CONSTRUCTIVE PERICARDITIS

Constrictive pericarditis is uncommon in children. It is characterized by a thickened and scarred pericardium due to acute or chronic pericardial inflammation. Diastolic filling of the ventricles is compromised. Tuberculosis is responsible for majority of cases. Other rare causes are cardiac surgery, radiation therapy, renal failure and connective tissue diseases.

Clinical Features

Signs and symptoms include fatigue, dyspnea, weight gain, abdominal distension and pedal edema. Examination shows pedal edema, prominent y and deep x descents in jugular veins, ascites and hepatosplenomegaly. Arterial blood pressure is usually normal. Kussmaul sign, which is failure of the venous pressure to decrease with inspiration, though not specific, is commonly seen. Diastolic pericardial knock, which is similar in timing to the third heart sound, corresponds to the abrupt cessation of the ventricular filling and is pathognomonic.

Diagnosis

Electrocardiography shows low voltage QRS complexes, T wave changes and is nonspecific. Chest X-ray shows pericardial calcification in less than half of these patients (**Figs 2A and B**). Pleural effusion may be present with normal or enlarged cardiac silhouette depending upon the extent of pericardial effusion. Echocardiography may demonstrate pericardial thickening and some pericardial effusion. Important 2D-echocardiography findings include a jerky interventricular septum, dilated inferior vena cava without respiratory variation and biatrial enlargement with normal left ventricular ejection fraction. Important Doppler echocardiography findings include decreased mitral inflow velocity with increased tricuspid inflow velocity in the first beat after inspiration and increased hepatic vein flow reversal in

expiration suggesting ventricular interdependence. Doppler tissue imaging shows a prominent E and gives an important point of distinction from restrictive cardiomyopathy. CT and MRI are sensitive investigations for determination of pericardial thickness and also help in differentiating from restrictive cardiomyopathy.

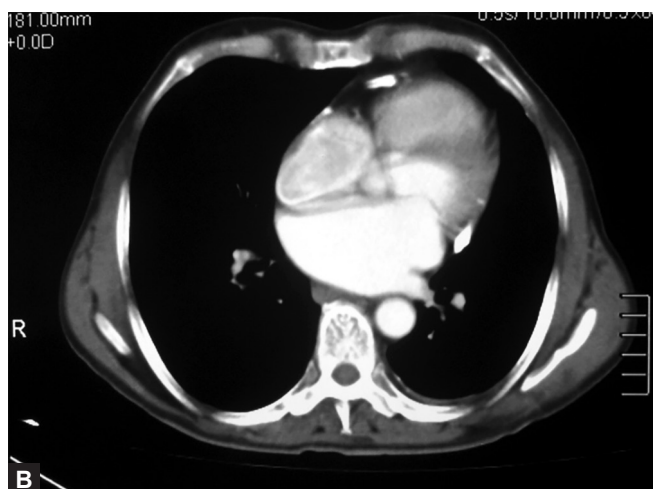
Cardiac catheterization with a predictive accuracy of around 75% is often done to confirm the diagnosis and exclude restrictive cardiomyopathy. It shows equal and elevated left and right atrial pressures, pulmonary capillary wedge pressure and ventricular end-diastolic pressures (usually more than one-third of right ventricular systolic pressure). A characteristic square root sign and discordance between right and left ventricular peak systolic pressures with respiration (right ventricular systolic pressure increases and left ventricular systolic pressure decreases during inspiration and vice-versa) are seen in the diastolic ventricular tracings.

Treatment

Pericardiectomy is the treatment of choice. Complete pericardial resection is recommended to prevent recurrences. Operative mortality is around 6% and is improving. Advanced age, higher New York Heart Association (NYHA) class and postirradiation etiology are poor prognostic factors.

IN A NUTSHELL

1. Viral pericarditis is the most common cause of acute pericarditis in children. Other less common causes are trauma, myocarditis, systemic lupus erythematosus (SLE) and purulent pericarditis.
2. Bacterial pericarditis usually occurs due to staphylococcal and *Haemophilus* infections. Appropriate antibiotics with urgent drainage of pericardial space are the standard of care. Some children would require surgical pericardiectomy.
3. Tubercular pericarditis is an important cause of constrictive pericarditis in India.
4. Noninfectious causes of pericardial involvement include systemic lupus erythematosus, rheumatic fever, systemic onset juvenile idiopathic arthritis, uremia and hypothyroidism.



Figures 2A and B (A) Lateral chest X-ray showing pericardial calcification in a patient of chronic constrictive pericarditis; (B) Computed tomography (CT) of chest showing pericardial and atrioventricular groove calcification in the same patient

MORE ON THIS TOPIC

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Chapter 40.37

Cardiac Dysrhythmias

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Cardiac dysrhythmias (arrhythmias are not an appropriate term as it implies absence of rhythm; however like so many other things it is unlikely to change) are no longer a subject that can be left to the cardiologists or the internists. Basic electrocardiographic (ECG) skills along with identification and management of common cardiac arrhythmias are essential for the pediatrician also.

Arrhythmias can occur in a variety of settings, acute or chronic, and present in several different ways. The worst presentation is sudden cardiac death (SCD) in a child who is otherwise completely healthy or has been leading a perfectly normal life post correction of a congenital heart defect, suddenly drops dead. Arrhythmias, we know can occur in normal hearts—diseases like long QT Syndrome (LQTS) and Brugada syndrome are seen all over the world with the same penetration. This chapter is focused on providing the reader a basic idea of how, what and where arrhythmias should be suspected and managed.

ARRHYTHMIAS ARE OMNIPRESENT

Arrhythmias can present in diverse ways—the simplest and most usual is a child complaining of something going wrong in his chest and when the parents put a hand on the chest they find the heart racing away. Obviously a child who has not reached the age to converse will not complain and maybe completely asymptomatic or crying inconsolably. A totally reverse situation is when we go hunting for an arrhythmia—to us it is imperative that every child on treatment for seizures should have an ECG done and history taking probe into similar events in other sibs. Every year we see at least one or two patients being treated for *refractory epilepsy* to be having a *channelopathy* like LQTS. Similarly, every child diagnosed as dilated cardiomyopathy (DCM) should have an ECG, because tachycardia related left ventricular dysfunction (tachycardiomyopathy [TCMP]) is among the treatable causes for an otherwise untreatable disease (**Box 1**: Case Vignettes). These examples emphasize on the need for constant improvement in our skills and abilities. We hope this chapter serves as a stimulus for pediatricians to sharpen their ECG skills.

BOX 1 Case Vignettes

Case Vignette 1

A 2-year-old child, with dilated cardiomyopathy with an ejection fraction of 15%, on routine medical management for over 6 months, was seen in our outpatient department a few weeks ago. The child had no congestive heart failure (CHF), was sleeping comfortably but had a heart rate of 130–140 bpm. Why should there be tachycardia in the absence of heart failure? Tachycardia is a response to CHF and not left ventricular (LV) dysfunction. Even so, the ECG of this child (this was the first ECG ever done since his illness!) showed normal PQRST relations (**Fig. 1**). A 24 hours Holter monitoring showed his heart rate was stuck at 130–140 bpm throughout day and night with very little circadian variation. An automatic atrial tachycardia was suspected, electrophysiological study done and an ectopic focus ablated. Heart rate came down to 80 bpm at rest and over 4–6 months, left ventricular function normalized.

Case Vignette 2

We have at least four families presenting in the last 6 months with multiple sudden infant death syndrome (SIDS) or a history of earlier children dying suddenly. At least one of them clearly has a LQTS identified (**Fig. 2**) when the child was put on a treadmill after repeated ECGs/Holter recordings had failed to show any abnormality. Even an epinephrine challenge had failed to identify a cause.

TACHYARRHYTHMIAS

A tachyarrhythmia is broadly defined as resting heart rates that are beyond the range of normal heart rate for the age of the child (**Table 1**).

GENESIS OF TACHYARRHYTHMIAS

The three basic mechanisms of tachyarrhythmias (re-entry, enhanced automaticity, and triggered activity) are outlined in **Table 2**.

Re-entrant Tachycardias

Re-entry or circus movement implies an impulse continuously going around a barrier. This occurs when an impulse proceeds in a differential manner along a pathway, either as a consequence of an anatomical barrier (e.g., scar) or a functional barrier (different electrophysiological properties). The following features essentially define a re-entrant circuit: (1) two distinct areas/pathways with different electrophysiological properties separated by (2) a *non-conducting, anatomic/functional barrier or area*, (3) unidirectional block, (4) a final common pathway, and (5) interruption of the re-entrant circuit at any point along its path should terminate the circus movement.

A typical example is an accessory pathway mediated tachycardia or a typical atrial flutter (AFL). The onset, offset and mechanism of an atrioventricular re-entrant tachycardias (AVRT) is shown in **Figures 3A to C**. The first beat shows a fused QRS wherein conduction through the pathway produces the delta wave but majority of QRS is inscribed rapidly through the His-Purkinje system (HPS). An atrial ectopic gets blocked in the accessory pathway (longer effective refractory period [ERP]) and renders it refractory for a short while. The impulse goes down the AV node-His bundle axis and reaches the accessory pathway from the ventricular end. This delay has allowed the pathway to recover its conduction and the impulse can now go retrograde into the atrium and reaches the AV node again, conduct orthodromically and sustains a *circus movement*. In case the delay has been insufficient for the AV node/His-bundle axis to have recovered conduction then the impulse gives only one extra P wave and no QRS and therefore no tachycardia. All re-entrant circuits therefore have to have a critical area of slow conduction that allows recovery of myocardial excitability to allow the circus movement to perpetuate.

Enhanced Automaticity

Several areas of the heart have had cells similar to the sinoatrial (SA) and AV nodes while in utero. In most cases these cells lose this ability of spontaneous automaticity as the fetus matures, thus leaving the SA node to be the dominant pacemaker. However, different reasons can make these areas fire again at a rate that is much more rapid than the normal rate. Such tachycardias arise from an ectopic location and do not obey the laws of re-entry. They may fire in short bursts lasting from a few seconds to hours or days. They are called incessant when they occupy more than 50% of the day. Atrial rates can be anywhere from 130/140 to more than 200/min. Typically, rates of 130–150 bpm are common, that may not cause symptoms. If this relatively fast rate persists for weeks to a few months it can lead to a reversible cardiomyopathy, called as *tachycardiomyopathy* (enumerated earlier). Atrial tachycardias (AT) form the most common example of enhanced automaticity and often present as TCMP in children.

Triggered Activity

This is the least common mechanism and is a term used to describe impulse initiation in cardiac fibers due to the occurrence of after-depolarizations (AD). These are oscillatory depolarizations that

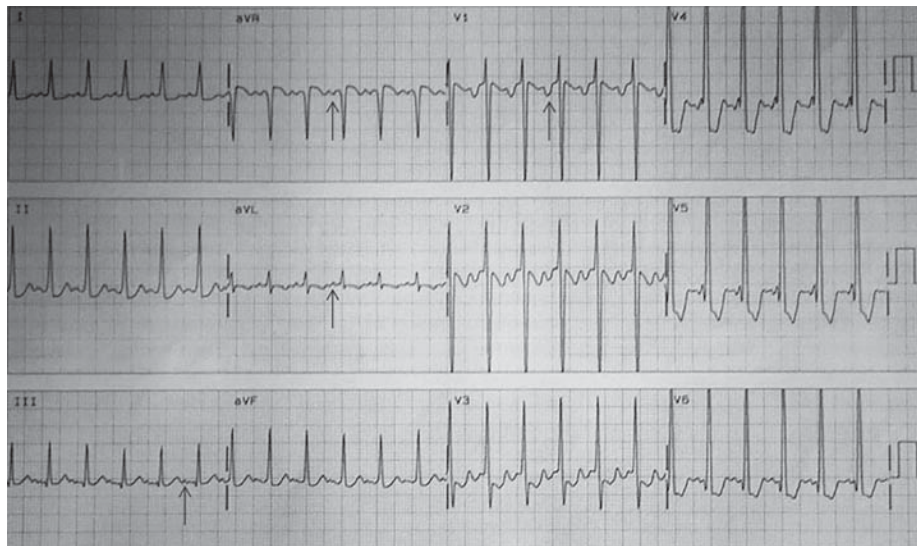


Figure 1 Narrow QRS tachycardia in a 2-year-old at approximately 150 bpm. Notice the PR is short compared to the RP, implying this is a long RP tachycardia. A casual look shows a normal PQRS, suggesting this is sinus tachycardia. However, the child was sitting comfortably and had no congestive heart failure (CHF). A closer look shows negative P in aVR, a small positive P in inferior leads and a deep completely negative P in V1 (arrows). In general, inferior leads should show a good upright P wave during sinus tachycardia. V1 should normally be a + or a \pm deflection as the sinus node is a posterior structure and the current comes towards V1. These clues along with the fixed rate point towards an automatic atrial tachycardia

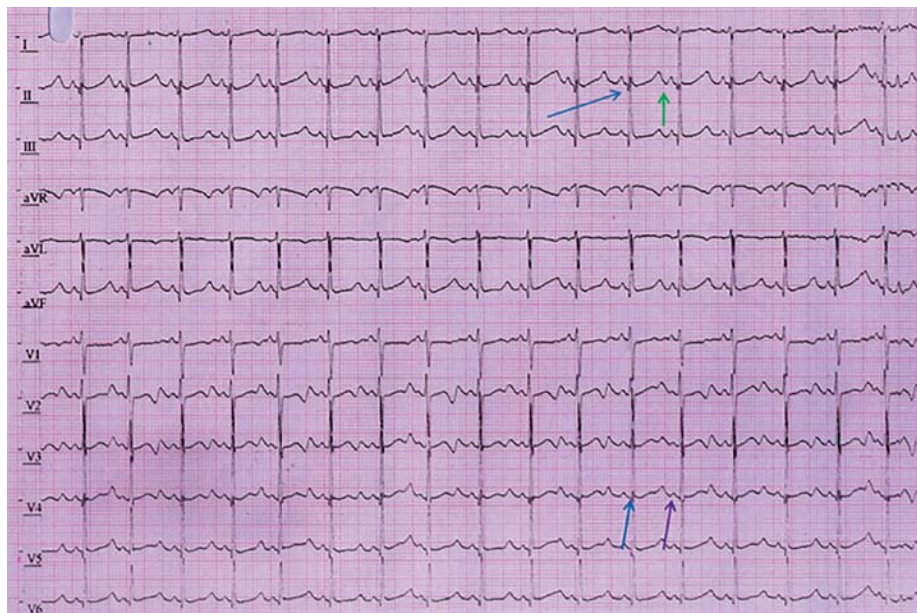


Figure 2 Twelve lead ECG taken during recovery phase of an exercise test. Blue arrows point to the beginning of QRS and green arrow at the end of T wave in Lead II. In Lead II, absolute QT is approximately 400 ms and RR is approximately 600 ms. QTc as per Bazett's formula comes to approximately 510 ms. Note the T wave notching (? U waves) in precordial leads V1-V4. If one labels them as U waves, the measurement should then be of the QTU interval. The QTU in V4 is 440 ms (purple arrow) which at an RR of 600 ms gives a QTc of 560 ms. QT interval can be different in between leads. While measuring ECG intervals like QT it is a good idea to keep either the beginning of Q or the end of the T on one of the thick lines of the ECG

follow the cardiac action potential. Two subclasses are traditionally recognized: (1) early (EAD), e.g., due to sotalol; and (2) delayed (DAD), e.g., digitalis toxicity and catecholaminergic polymorphic ventricular tachycardia (CPVT).

ETIOLOGY

Arrhythmias occur because of a large variety of reasons but most often the underlying heart is structurally normal. However,

abnormal hearts with depressed systemic ventricular function are also highly prone to get arrhythmias.

Structurally Normal Heart

- Most supraventricular tachycardias (SVTs) like AVRT, AV nodal re-entrant tachycardia (AVNRT) and ectopic atrial tachycardias (EAT) occur in a structurally normal heart.
- Some ventricular tachycardias (VTs) occur in structurally normal hearts. Common examples include those arising from

Table 1 Normal resting and exercise heart rates (beats per minute) for various ages

Age	Resting (sleeping)	Resting (awake)	Crying/exertion
Newborn	80–160	100–180	Up to 220
1 week to 3 months	80–200	100–220	Up to 220
3 months to 2 years	70–120	80–170	Up to 200
2–10 years	60–90	70–110	Up to 200
10 years to adult	50–90	55–90	Up to 200

Table 2 Basic mechanisms of arrhythmias and their common examples

- Re-entrant
 - AV re-entrant tachycardias (AVRT)
 - WPW, Concealed bypass tract, PJRT, Mahaim fibers
 - AV nodal re-entrant tachycardia (AVNRT)
 - Atrial flutter and intra-atrial re-entrant tachycardia (IART)
 - Atrial fibrillation
 - Scar related ventricular tachycardias
 - Fascicular VT, Torsades-de-pointes
- Enhanced automaticity
 - Ectopic atrial tachycardias (EAT)
 - Chaotic atrial rhythm
 - Junctional ectopic tachycardias
 - Congenital
 - Postoperative
 - Ventricular tachycardias
 - Hamartomas, rhabdomyomas
 - Inappropriate sinus tachycardia
- Triggered activity
 - RVOT tachycardia
 - Digoxin toxicity

Abbreviations: WPW, Wolff-Parkinson-White syndrome; AV, atrioventricular; PJRT, permanent junctional reciprocating tachycardia; RVOT, right ventricular outflow tract; VT, ventricular tachycardia.

the fascicles of the left ventricle (fascicular tachycardia) and due to channelopathies like LQTS, Brugada syndrome, CPVT, etc.

- Metabolic and electrolyte derangements such as hyperkalemia, hypokalemia, hypothermia, hypoxia.
- Drugs like digoxin, adrenergic agonists, antiarrhythmics (most antiarrhythmic drugs are capable of causing new arrhythmias). Drugs like sotalol, terfenadine (an obsolete antihistaminic) that cause QT prolongation can precipitate torsades—these arrhythmias are labeled as *proarrhythmias*.
- Increased intracranial pressure.

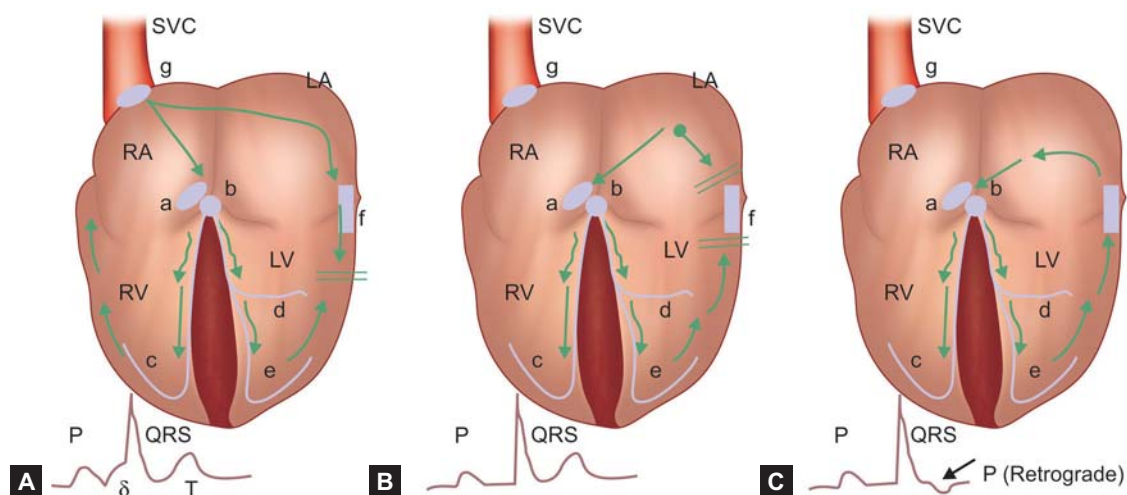
Structural Heart Disease

- Primary atrial tachycardia (AT), atrial flutter (AFL), junctional ectopic tachycardia (JET) and VT may sometimes occur in acute postoperative settings.
- AFL and atrial fibrillation (AF) occur largely in the presence of structural heart disease. While AF typically occurs due to a large left atrium in rheumatic mitral valve disease, flutter can be seen in patients of atrial septal defects or postincisional surgical scars.
- Cardiomyopathies may also be associated with atrial and ventricular arrhythmias leading to VTs and sudden death.
- Cardiac tumors like rhabdomyoma, fibromas often lead to VT.

CLINICAL PRESENTATION AND DIAGNOSIS

Symptoms

These depend on the age of the child, underlying structural heart disease if any, duration of the tachycardia and parental education/awareness about the disease. Neonates and infants may present with tachypnea, poor feeding, vomiting, excessive crying or restlessness or excessive somnolence. Older children may complain of palpitations, chest pain, syncope or sometimes are unable to describe the peculiar feeling. Severe forms of arrhythmia can produce cardiovascular collapse, CHF, SCD and SIDS. Persistent SVT/VT can produce a DCM-like picture.



Figures 3A to C Tachycardia mechanism: re-entry (a: AV node, b: His-bundle, c: Right bundle, d: Left anterior fascicle, e: Left posterior fascicle, f: Left lateral accessory pathway (AP), g: SA Node). (A) Figure shows impulse originating from SA node (green arrows) and going to the ventricle through the His-Purkinje System (HPS) and the accessory pathway lying at the lateral mitral annulus (red, f). The ECG beat under it shows a short PR and the delta (δ) wave formed by the myocardial depolarization of the local muscle at the site of the accessory pathway insertion. For clarity we have shown the delta (δ) wave prominently—however, in general left lateral pathways do not have such a prominent delta (δ) wave as by the time the impulse reaches the pathway most of the ventricle has already got depolarized through the HPS; (B) Figure shows an atrial ectopic coming from the LA that gets blocked in the pathway but conducts through the HPS. Thus, there is no delta (δ) wave in the ECG. The beat comes back to the AP but finds the pathway still refractory and thus cannot get to the A again—hence there is no tachycardia; (C) Figure shows the same thing as in B, the only difference being that the AP has recovered. The beat goes back into the atrium (the negative P shows retrograde conduction) and reaches the AV node again. If the AV node has recovered by this time, it starts a tachycardia

Clinical Examination

If the physician is lucky, he may see the child during the arrhythmia, and note the abnormal heart rate and rhythm. A scar suggestive of previous surgery may suggest underlying heart disease. A careful examination of the precordium, neck vessels and hepatomegaly will point towards heart failure as a cause or effect of tachyarrhythmia. Observing the neck even in an infant is very useful to detect an ongoing tachycardia. The precordium may be hyperdynamic. Often the examination will be normal as there is no underlying structural heart disease.

SVTs are generally benign except for the symptoms that they produce. Orthodromic SVT in infants and children can occasionally be very rapid (ventricular rates of 250–300/min) and may lead to syncope and death. Most SVTs are *short RP*, implying PR interval will be very long thus making the atrium contract at an inappropriate time, often in ventricular systole against a closed AV valve. This, along with the rapid rate that leads to decreased cardiac output and stimulation of renin-angiotensin system leads to CHF sometimes within 3–4 hours of onset of tachycardia. Infants are typically more susceptible to go into CHF that is not due to ventricular *systolic* dysfunction and should not be labeled as TCMP (see earlier discussion). This CHF resolves within minutes of tachycardia termination and does not prevent use of β -blockers.

DIAGNOSIS OF ARRHYTHMIA

Even in the absence of the tachyarrhythmia, the ECG may point towards a specific disorder (e.g., Ebstein anomaly, Brugada syndrome, LQTS, short QT syndrome, digitalis toxicity, hypokalemia). Though QRS width is dependent on age, broadly a

QRS more than 120 ms is a wide QRS tachycardia. In general, SVTs are narrow QRS and VTs are broad QRS. However, a fascicular VT can be narrow and an antidromic tachycardia through an accessory pathway can be wide. Rate related aberrancy is uncommon in children and aberrancy if seen is due to pre-existing bundle branch block as in patients operated for tetralogy of Fallot (TOF). A standard dictum for a wide QRS tachycardia is not to use calcium channel blockers.

If a child is seen in a clinic/hospital in tachycardia every effort should be made to do a 12 channel ECG with simultaneous acquisition of all leads in a 12 \times 1 format (**Fig. 4**). Further, a continuous ECG should be recorded while doing any maneuver or injecting adenosine. Adenosine gives a very unpleasant feeling and most children move at that time, spoiling the ECG trace. We often give a sedative before giving adenosine so that a good record can be obtained. These recordings are very valuable as they help in making a diagnosis and long-term management. Ensure these recordings are either photocopied or digitized as thermal printouts can fade overtime. Recording at the rate 50 mm/s speed is of no use in identifying the tachycardia as the P waves get stretched and become indistinguishable from T or U waves. It may sometimes be useful when the tachycardia is extremely rapid, more than 260–270 bpm. A 50 paper speed is predominantly useful when one has to serially monitor QRS or QT duration over long-term.

Holter Monitoring

Continuous ambulatory 24–72 hours ECG recording can be used to pick-up episodes of tachycardia and to determine a symptom correlation. Obviously, infrequent episodes will not be picked up by such a short recording. More often a Holter can be useful

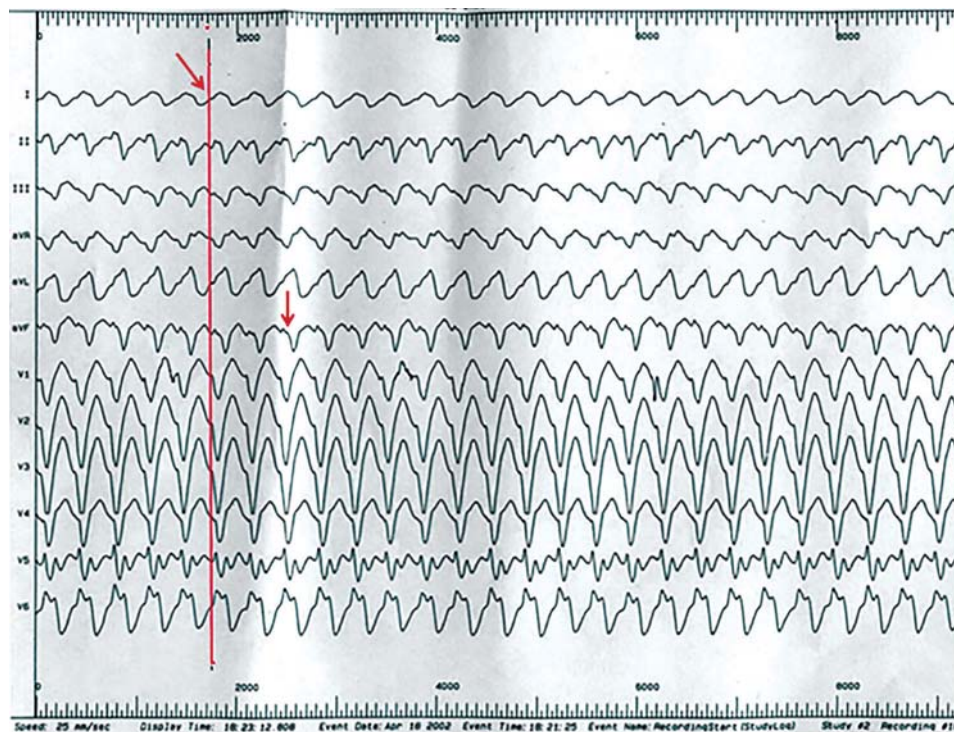


Figure 4 Importance of the 12 \times 1 stacked format ECG in arrhythmia diagnosis. Broad QRS tachycardia in a 12-year-old child. A line has been drawn on the QRS onset based on leads V1–V3 where it is best seen. Top arrow points to lead I QRS onset—seen in isolation it would have been impossible to say where QRS started. Bottom arrow on lead aVF, pasted onto a QRS away from the line for clarity. Notice the small positive wave just after T. This is not the P wave but is part of the QRS—on a single channel this would have been taken as P wave leading to an incorrect diagnosis. This is a broad QRS tachycardia with left axis and left bundle branch block (LBBB) morphology—differential diagnosis of such a tachycardia is— (a) Monomorphic ventricular tachycardia (VT) coming from the RV inflow, classical of arrhythmogenic right ventricular cardiomyopathy (ARVC), (b) Bundle branch re-entrant VT, an uncommon arrhythmia in children, (c) antidromic tachycardia through a Mahaim pathway, (d) orthodromic supraventricular tachycardia (SVT) with LBBB aberrancy

in diagnosing an automatic tachycardia (as in TCMP), pick-up intermittent pre-excitation, record ambient ventricular ectopy in the presence of structural heart disease especially post-TOF repair. Another setting wherein they may be useful is when looking for channelopathies like LQTS wherein the QT prolongation is often not present all the time. Systemic ventricular dysfunction or post-TOF repair children often get frequent ventricular ectopics as isolated beats, couplets, bigeminy, triplets, etc.—such patients maybe at a higher risk of SCD and may need more detailed evaluation. Too often we have seen Holters being prescribed for palpitations occurring once in a few months or even as a preoperative screening tool—Holter monitoring in children is not easy and is expensive too.

Cardiac Event Recorders/Mobile Cardiac Telemetry

These recorders in general are capable of recordings up to 1–2 weeks, generally of a single or at best two channels. They are useful if symptoms are occurring once in 1–2 weeks. With mobile technology integrating with ECG, devices are available which can be kept at home with the patient or worn 24/7. These devices will record a single channel on command and transmit through Bluetooth or similar technology to a mobile and then a remotely stationed server. We expect this technology and its variants will revolutionize arrhythmia detection, monitoring and management with remotely stationed experts giving real time feedback.

Exercise Testing

Exercise testing perhaps should be routinely done in evaluation of syncope, family history of sudden cardiac death or symptoms related to exercise. It may help in risk stratification of Wolff-Parkinson-White (WPW) syndrome and is useful in assessing adequacy of β -blockade and drugs like flecainide that show use dependence. LQTS, CPVT, arrhythmogenic right ventricular cardiomyopathy (ARVC) are typical settings wherein exercise test can help in the diagnosis (see earlier, **Fig. 2**). We have been able to make even 5–6 year-old do a short exercise ECG when needed.

Intracardiac Electrophysiological Studies

Intracardiac (or transesophageal in children) electrophysiological studies (EPS) have been available for a fairly long time and are supposed to be the most definitive tool in arrhythmia management. EPS has no role in evaluating bradycardias, be it Sick sinus syndrome or a 2:1 AV block. It is occasionally needed for risk stratification of WPW syndrome in children. In general, these studies are now done as a part of treatment wherein catheter ablation is performed simultaneously. Diagnostic EPS has a very limited role in the current era. VT induction is sometimes attempted in postoperative TOF patients to identify patients at high-risk of SCD. In adults, VT induction by EPS has been a debatable topic since over 30 years and will probably remain so till more reliable tools are invented.

SPECIFIC ARRHYTHMIAS AND THEIR MANAGEMENT

Common supraventricular arrhythmias are listed in **Table 3**.

Sinus Tachycardia (ST)

Sinus tachycardia is the most common dysrhythmia seen in practice—mostly it should not be called a dysrhythmia as it is physiological and appropriate for the need. There are two reasons for highlighting ST—(1) it is the single most important confounder in diagnosing an arrhythmia and (2) occasionally, the sinus node may fire at a higher rate than what is expected. When ST is not associated with a disease or an identifiable cause

Table 3 Supraventricular tachyarrhythmias

• AV Re-entrant tachycardia (73.2%) – Concealed bypass, WPW, PJRT, Mahaim fibers
• AV nodal re-entrant (12.5%)
• Primary atrial tachycardia (14.3%) – Atrial flutter and IART – Ectopic atrial tachycardia – Chaotic atrial rhythm – Atrial fibrillation
• Junctional ectopic tachycardia – Congenital – Postoperative

Abbreviations: WPW, Wolff-Parkinson-White (WPW) syndrome; PJRT, permanent junctional reciprocating tachycardia; IART, intra-atrial re-entrant tachycardia.

and the underlying heart is normal, it is labeled as *inappropriate sinus tachycardia*. This condition is difficult to recognize, diagnose and manage. Sinus tachycardia is a normal response to situations like exertion, fever and anxiety or more pathological states like hypotension, thyrotoxicosis, anemia, congestive heart failure and drugs like atropine and catecholamines. The treatment lies in the diagnosis and management of the underlying etiology. Following points are useful to differentiate sinus tachycardia from SVT:

- P waves with a morphology suggesting an abnormal origin—sinus P waves in lead aVR (in a solitus heart) should always be negative and should be positive in inferior leads
- Gradual onset and offset of tachycardia
- Presence of sinus arrhythmia (heart rate changes associated with breathing), though this maybe blunted
- PR prolongation during tachycardia goes against sinus tachycardia as sympathetic stimulation causing the ST should improve AV conduction and shorten it
- *Adenosine challenge* Sinus tachycardia rarely shows an AV block with an intravenous adenosine bolus while atrial tachycardia's generally show a transient AV block. The slowing/transient block also allows evaluation of P wave morphology as discussed earlier. Very sick children with borderline hemodynamics should not be given adenosine challenge as it leads to transient cardiac ischemia that can tilt the balance unfavorably.

Atrial Flutter

It is a re-entrant tachycardia usually confined to the right atrium wherein the circuit goes around the tricuspid annulus. It rarely occurs in the presence of normal heart, except in neonates and the elderly.

Neonatal atrial flutter is an intriguing entity. Most often, underlying structure and function is normal. The usual AFL is cavotricuspid isthmus (CTI) dependent which is the critical slow conducting zone (**Fig. 5**). Since it is a re-entrant arrhythmia one cannot pin point a location of origin. Earlier on a *typical flutter* was defined as one circulating in a counterclockwise direction around the tricuspid annulus in the frontal plane and *atypical* if it was in a clockwise direction. After recognizing that both these forms were essentially the same circuit and could be treated by ablating the isthmus, this terminology has become ambiguous. Most electrophysiologists call both these flutters as typical and flutters that do not use the CTI as atypical. Such atypical non-CTI dependent flutters are often seen to be going around postsurgical scars or in diseased atria. ECG in typical AFL shows the following:

- Dot regular and absolutely identical flutter waves (saw-tooth like P waves)

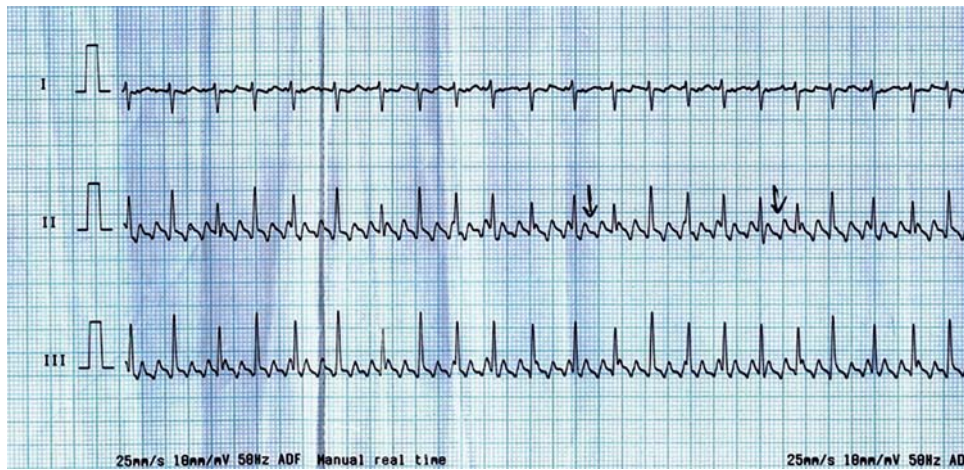


Figure 5 Three-channel ECG showing atrial flutter in a 3-day-old child. Note the typical saw tooth pattern which is more evident when the AV block increases to 3:1. There is no isoelectric baseline as the re-entrant circuit goes around the tricuspid annulus and there is no time in the cardiac cycle when the atria are electrically silent. In neonates, flutter may conduct 1:1 leading to a ventricular rate of around 300/min. This may obscure the saw tooth pattern and it may be difficult to diagnose flutter. IV Adenosine can be used to create a transient AV block which reveals the flutter waves. Flutter is a macro re-entrant tachycardia going around the tricuspid annulus in the right atrium

- Flutter wave rates are 250–350/min, often 300 bpm
- A fixed AV block (2:1 or 4:1) leads to a slower ventricular rate, typically 150/min
- A distinctive feature is the absence of an isoelectric baseline between the P waves.

A ventricular rate of 150/min with the P wave falling right in the middle of the 2 QRS complexes should arouse suspicion of a typical atrial flutter (rule of Bix).

Treatment

Atrial flutter is not easily amenable to drug therapy and therefore transesophageal pacing or DC cardioversion (DCCV) may be necessary. This is often the case in neonates in view of their hemodynamic instability, wherein once terminated it usually does not recur. Peculiarly, digoxin has been shown to be useful in preventing recurrences. Radiofrequency ablation in CTI dependent flutters has a high rate of success (90–100%) and may sometimes be needed if all drugs fail in preventing recurrences or terminating it.

Atrial Fibrillation

Characterized by an extremely fast atrial rate (350–600 per minute) with an irregularly irregular ventricular response, AF almost always occurs in the presence of structural heart disease with chronic rheumatic mitral valve disease being the most common cause in India. AF is uncommon in children and is important only in older children with WPW syndrome wherein it can lead to a rapid ventricular response through the accessory pathway and cause SCD. This may also happen if intravenous (IV) calcium channel blocker (CCB)/digoxin and sometimes even adenosine are given for an older child with WPW syndrome. It is mandatory to have a defibrillator ready when one gives IV adenosine for terminating SVTs in children with WPW syndrome. Since this may not be known in the first episode it is good practice to do this routinely.

Chaotic Atrial Rhythm

Also called as multifocal atrial tachycardia, chaotic atrial rhythm (CAR) is seen in early infancy (mostly < 3 years of age). It generally has a benign course and may be seen in children with dilated cardiomyopathy. ECG shows (1) multiple (at least three) distinct P-wave morphologies; (2) irregular P-P intervals; (3) isoelectric baseline between P-waves; and (4) ventricular rate more than

100 beats/min. It is a difficult tachycardia to treat and should best be dealt by an arrhythmia expert. One can try AV nodal blocking drugs to slow down the ventricular rate or Class Ic/III drugs.

SUPRAVENTRICULAR TACHYCARDIAS

These tachycardias were labeled earlier as junctional tachycardias as no P waves were seen during the tachycardia and therefore they were thought to be coming from the junction. Electrophysiological studies showed that P waves were generally hidden in the QRST segments; these tachycardias were thus labeled as *supraventricular tachycardias*.

There are three tachycardias that generally constitute this group: (1) AV nodal re-entrant tachycardia, (2) AV re-entrant tachycardia, and (3) automatic atrial tachycardia. The term *supraventricular tachycardia* is now used to encompass these tachycardias even though AVRT cannot occur without ventricular involvement. These tachycardias are in general narrow QRS and can be terminated by either drugs acting on the atrium or on the AV node. All tachycardias that arise from the ventricle are always (except for fascicular VT) broad QRS and are labeled as *monomorphic* or *polymorphic* ventricular tachycardia depending upon the ECG morphology of the tachycardia beats. Most SVTs, especially the re-entrant variety are not regular and in children show equal atrial and ventricular rates due to a *brisk* AV node.

Atrioventricular Re-entrant Tachycardia (Re-entrant Tachycardia over Accessory Pathway, Wolff-Parkinson-White Syndrome)

Accessory pathways are muscle fibers that connect the atrium or AV node to the ventricle outside the normal AV nodal-His-Purkinje conduction system (AVN-HPS). Conduction over accessory pathways may be anterograde (from atrium to ventricle) or retrograde (from ventricle to atrium). Anterograde conduction results in ventricular depolarization outside the His-Purkinje conduction system. Since ventricular conduction is slow, it inscribes a low frequency signal that results in a slow up stroke (slur) known as a *delta wave*. This pathway is thus *manifest* (**Fig. 6**). A pathway that only conducts from ventricles to atria (retrograde) will not manifest itself as a delta wave/pre-excitation and is thus known as *concealed*.



Figure 6 Wolff-Parkinson-White (WPW) syndrome in a child with recurrent episodes of supraventricular tachycardia (SVT). Note the delta waves in inferior leads. It is not normal to have a negative QRS in inferior leads. The P waves are relatively small (blue arrows) and so the short PR is not seen in all leads. The delta waves (red arrows) are negative in inferior leads, positive in I, V2. Based on this we found a pathway in the os of the coronary sinus where it was ablated using low powers. However, pre-excitation recurred after a few days, though the child has not had tachycardia again. Given the increase in incidence of atrial fibrillation with age, one may still have to ablate the pathway if its effective refractory period (ERP) is short, as it can lead to VF

The term *Wolff-Parkinson-White syndrome* is used when a manifest pathway leads to ECG changes and symptomatic tachycardia. An accessory pathway that does not give rise to symptoms or tachycardia is labeled as asymptomatic pre-excitation and not asymptomatic WPW. More recently it has been found that a manifest right sided pathway leads to dyssynchronous activation of the ventricles that can lead to severe left ventricular dysfunction similar to what happens in left bundle branch block. This DCM can be completely reversed by ablating the pathway and is different from TCMF.

Tachycardia in the presence of a pathway is mostly orthodromic, implying an atrial ectopic finds the accessory pathway refractory and travels down the HPS. Since this beat did not go to the ventricle through the pathway, there will be no delta wave on the ECG. The wave front exits into the ventricle through the HPS and proceeds retrogradely towards the base of the heart where it finds the accessory pathway no longer refractory and thus lets the impulse into the atrium. If the adjoining atrium and AVN-HPS have recovered the beat will go down into the ventricle and setup the tachycardia. The same can happen when a ventricular ectopic finds the HPS refractory and goes to the atrium through the pathway and lead to a circus movement. Uncommonly, the pathway may be having a shorter refractory period than the AVN-HPS and in this case the atrial ectopic goes down the pathway and comes up the AVN-HPS leading to an antidromic tachycardia. This tachycardia is a broad QRS one as the myocardium gets depolarized muscle to muscle starting eccentrically at the site of pathway insertion into the ventricle. This is exactly how a VT would behave if it was to start from the same muscle area—thus an antidromic tachycardia looks more like a VT on the ECG and behaves like one too. The long conduction time in the ventricle along with dyssynchronous activation often leads to hypotension and the treatment should be DCCV at the earliest. Adenosine may terminate the tachycardia by

blocking its retrograde conduction through the AV node.

Electrocardiographic Recognition, Orthodromic AVRT (Fig. 7)

- Narrow QRS, dot regular tachycardia with a rapid initial upstroke/downstroke
- Retrograde P wave occurs after QRS complex, in the ST segment, or early in the T wave occasionally causing ST segment depression or notching
- Presence of AV or VA block/dissociation rules out bypass mediated tachycardia
- QRS alternans and ST depression may be seen in same patients.

Electrocardiographic Recognition, Antidromic AVRT

- PR interval less than 120 ms during sinus rhythm. P waves are difficult to recognize as the QRS rate is often 250 and above, and the QRS is extremely broad
- QRS complexes are broad with a slow rise like a delta for the entire upstroke
- QRS complex duration exceeding 120 ms
- Secondary ST-T wave changes, directed opposite in direction to the major delta and QRS
- Regular QRS tachycardia, matching the pre-excited sinus rhythm ECG to an extent.

Not all pathways behave in the same fashion. Mahaim pathways are fibers that connect the atrium to the right bundle and lead to a wide QRS tachycardia of left bundle branch block (LBBB) morphology. The tachycardia has a LBBB morphology because conduction from right atrium goes directly into distal right bundle which activates the RV first and then LV. These pathways do not conduct retrogradely and are decremental in nature. The Lown-Ganong-Levine (LGL) syndrome comprises of tachycardia in the

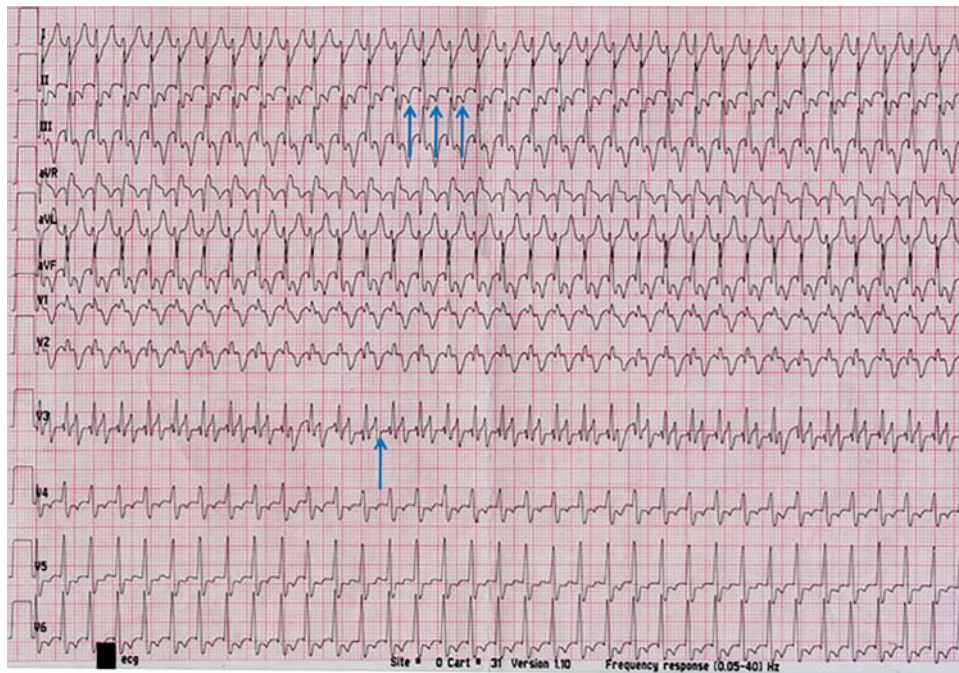


Figure 7 Orthodromic AVRT at rate of approximately 235/min in a patient with Ebsteins anomaly and a huge right atrium. Note the arrows in lead II point to a sharp deflection after QRS-T waves are generally not this sharp. Note in V3, there is a very large P wave after the QRS. This is because of the large RA in an Ebsteins patient. This is a short RP tachycardia as the PR interval is more than 50% of the RR interval

presence of a short PR with a normal QRS and was believed to be due to fibers that either completely or partially bypass the AV node. These fibers do not insert into the ventricle or fascicle and hence do not lead to a delta wave. No specific tachycardia has been linked to these fibers and hence this entity is no longer considered clinically important.

An important tachycardia in neonates is the permanent junctional reciprocating tachycardia (PJRT) that is often incessant and frequently associated with left ventricular dysfunction. PJRT occurs because of a concealed bypass tract mostly located in the right posteroseptal region that conducts decrementally. Hence, when the propagating wavefront reaches the pathway, instead of going into the atrium rapidly it goes slowly. This allows the atrium and the AV node enough time to recover and thus perpetuate the tachycardia, making it incessant. This tachycardia is a classical long RP tachycardia as the maximum delay is in conduction from ventricle to the atrium and thus RP becomes more than PR. Since the pathway mostly lies in the posteroseptal region the wave front breaks low into the atrium and gives negative P waves in inferior leads. Typically, the tachycardia keeps breaking and restarting and therefore drugs like adenosine or DCCV are of no use. Since there is significant ventricular dysfunction associated with the tachycardia it may not be possible to give β -blockers. In most cases, one ends up using IV amiodarone followed by oral therapy. The pathway may lose conduction spontaneously overtime and the tachycardia thus may go away with time. RF ablation may be needed in some cases when the tachycardia is refractory.

Atrioventricular Nodal Re-entrant Tachycardia

The human AV node is a complex structure with a compact part, two inferior extensions and multiple transitional components that channelize conduction. This leads to uneven conduction creating a *functional dual physiology* that typically increases with advancing age. Thus, there is a *fast* pathway that lies superiorly and shows faster conduction with a longer refractory period compared to the inferiorly lying *slow* pathway. This results in formation of a circus

movement involving parts of the AV node and atrium, causing different tachycardias that bear specific characteristics. This tachycardia called AVNRT can be typical or atypical depending on how the conduction proceeds along these *pathways*. The typical variety shows antegrade conduction down the slow pathway and retrograde conduction via the fast pathway. The His-bundle and ventricle are activated passively and are not part of the tachycardia circuit. This tachycardia is rarely seen in infants and increases in frequency with increasing age, outstripping AVRT as the dominant mechanism in adults. In children, it shows the following characteristics:

- Usually there is 1:1 AV conduction with ventricular rates more than 200–250 beats/min.
- The QRS complex is normal in contour and duration, unless functional aberrant ventricular conduction or a previous conduction defect exists, which is uncommon in children.
- P waves are generally buried in the QRS complex. Often, the P wave occurs just after the end of the QRS and causes a subtle alteration in the terminal QRS complex that results in a pseudo-S or pseudo-r', which may be recognized only on comparison with the QRS complex in normal sinus rhythm (**Fig. 8**).
- AV nodal re-entry begins abruptly, usually after a premature atrial contraction (PAC) that conducts with a prolonged PR interval.

Ectopic/Automatic Atrial Tachycardia

Atrial tachycardia is the second most important cause of a regular SVT in children—in older children and adults its incidence is much lower than AVNRT. Most atrial tachycardias are due to enhanced automaticity wherein some part of the *atria* starts firing abruptly. More recently it has been found that even the venous structures like pulmonary veins, superior vena cava (SVC) and coronary sinus can lead to an automatic tachycardia. In general, such automatic tachycardias occur from specific locations, probably those which in utero had *sinus node* like cells that failed to involute completely.

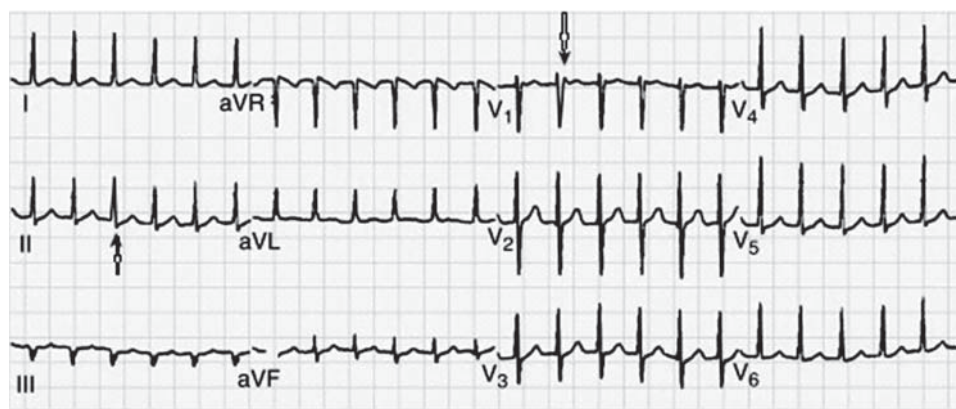


Figure 8 Narrow QRS supraventricular tachycardia (SVT) at 200/min. No P waves are seen—the retrograde P waves occur so early that they get buried within the QRS. Since the retrograde breakthrough occurs from the AV node which is a relatively posterior/inferior structure in the atria, P waves are negative in inferior leads appearing as pseudo-S waves. Note the Pseudo-r' waves in lead V1 (arrows) that are also P waves

Secondary causes like myocarditis, elevated atrial pressures and atrial stretch can also trigger some areas to fire rapidly.

Given that AF is very uncommon in children it may be of interest to pediatricians that the common garden nonvalvar AF actually starts from a pulmonary vein muscle sleeve that starts discharging very rapidly. This very high rate gradually leads to atrial dilatation and structural changes which then perpetuates AF. This is why *pulmonary vein isolation* is now first-line treatment for AF. Given that atrial tachycardias are nonre-entrant, the ECG and its management is quite different from the other SVTs. Depending on the site of the focus causing tachycardia following features are observed:

- The tachycardia is often a long RP tachycardia. This is because PR interval remains normal or may increase marginally if the rate is very high. However, short RP intervals do not rule out an EAT.
- Usually has an abnormal P-wave axis (e.g., inverted in the inferior leads II, III and aVF when the focus is lying in the low atrium). P waves should be seen in Leads aVR, Inferior and V1 (see earlier discussion on sinus P waves), to determine whether they are sinus or not sinus. This may not be easy in a fast tachycardia wherein the P gets buried into the T.
- P wave morphology may be abnormal—it may be narrower or broader or more peaked.
- QRS complexes have a normal morphology unless there is a pre-existing bundle branch block, accessory pathway, or rate related aberrant conduction. It is possible to see a 2:1 AV response or even higher grade of block. Presence of any AV block during a narrow QRS SVT excludes AVRT.
- Isoelectric baseline is seen unlike AFL.
- Minimal diurnal variation in the rate—most often the atrial rate remains fixed at a single value or varies by a few milliseconds. Some EATs maybe more sympathetic dependent and show rate variation in the range of 30–40 bpm. A tachycardia that is disproportionate to the child's clinical condition is often an EAT.
- *Adenosine challenge*: May terminate nearly 30% of EATs. Otherwise shows several short periods of AV block with the A rate remaining unchanged. Here lies the importance of recording this on paper as the monitor may give an incorrect impression of the tachycardia stopping or restarting. This happens because the most evident wave on the monitor is the QRS which actually decrease because of the AV block.

Figure 9 provides ECG clues to identify the SVT mechanism.

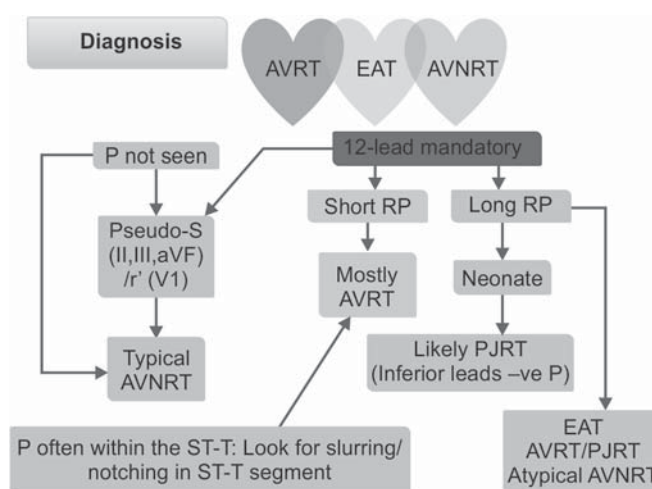


Figure 9 Paroxysmal supraventricular tachycardia (PSVT): ECG diagnosis algorithm. Every effort should be made to do a 12 lead ECG. In general these three tachycardias are dot regular, though AV block may occur with an EAT that could make the QRS irregular. The most important part of the diagnosis is to hunt out the P waves (see text). Once P waves have been identified it becomes fairly simple. Other clues that may help are: (1) Presence of AV block excludes AVRT, (2) QRS alternans favors AVRT, (3) ST, T depression favors AVRT
Abbreviations: AVRT, atrioventricular re-entrant tachycardia; PJRT, permanent junctional reciprocating tachycardia; EAT, ectopic atrial tachycardia; AVNRT, atrioventricular nodal re-entry tachycardia.

Acute Management of Supraventricular Tachycardia

The acute management depends on underlying structural heart disease, pre-excitation, age of the child, likely mechanism of tachycardia, hemodynamic status, especially heart failure due to a mechanical AV dyssynchrony and the fast rate itself. Left ventricular function cannot be assessed during the tachycardia because of the fast rate, incomplete filling of the ventricles an altered AV relationship and other factors. Based on the earlier factors and the child's blood pressure, peripheral signs of low cardiac output, etc., management options are chosen.

It is essential in today's era that a good quality simultaneously acquired 12-lead ECG in the 12 × 1 format is recorded prior to any treatment and also when the treatment is going on. Thus, if there

are facilities to record everything in a 12-lead format on the monitor itself that would suffice. If not, it is ideal to keep a 12-lead ECG running whenever an *intervention* is done. In a hemodynamically stable child, vagal maneuvers could be tried before pharmacologic therapy, though success rates are low and most of us in practical settings hardly ever use it.

Vagal Maneuvers

Traditionally include ocular pressure, Valsalva/pressure on infant's abdomen, carotid sinus massage, gagging and icebag application/Dive reflex. *Ocular pressure is contraindicated in infants and children less than 2 years and in general is no longer advocated for even adults.* The same applies for pressure on the abdomen especially if liver is enlarged, that is not uncommon in infants with a SVT lasting over 3–4 hours. Carotid sinus massage is acceptable in older children but has to be done correctly. Too often the pressure is either inadequate or improperly applied. It is important to apply pressure good enough to dent a tennis ball but not obliterate the pulse. Pressure should be applied towards the vertebral column, i.e., posteromedially and not more than 5 seconds at one time. It can be repeated on the other side or on the same side. Icebag application if done properly has been shown in some studies to have a 90% efficacy rate. A plastic bag of sufficient size to cover the entire face should be filled with one-third ice, one-third water and applied on the child's face for 10 seconds. It can be reapplied after a minute or so if the first application fails. The traditional method of immersing the child's face into cold water should not be attempted and applying a cold wet towel to the face is not effective. It is important that one wipes the face after the icebag application with a warm cloth to avoid cold panniculitis. The technique is rather cumbersome and not as successful as described by some. However, it has been seen that this in combination with adenosine (either simultaneous or immediate postapplication) maybe successful when the initial adenosine failed.

Adenosine

Intravenous adenosine is the treatment of choice for SVT because of its ultrashort duration of action and therefore a low incidence of complications. It has a 95% efficacy in re-entrant SVTs that is slightly higher than calcium channel blockers that are also effective in over 90% of cases.

Serious adverse effects occur occasionally and include: apnea/bronchospasm, accelerated and prolonged ventricular rhythm, prolonged asystole, proadrenergic effect enhancing AV conduction and shortening of the ERP of the accessory pathway leading to ventricular fibrillation (VF). It is important that the drug is pushed as a bolus and 5–10 mL of saline pushed in immediately after it. No blood should be allowed to come in contact with the drug outside the body as that metabolizes the drug instantly rendering it ineffective. Hence, new syringes and a new three-way need to be taken for every push. Although doses of 0.05 mg/kg may be effective and most texts generally recommend using 0.1 mg/kg and escalating up if tachycardia does not respond, we prefer to straightaway use a dose of 0.15–0.2 mg/kg, that is more predictable and saves on the cost and unpleasantness of repeated administration.

Intravenous Verapamil/Diltiazem

Intravenous verapamil/diltiazem has a more than 90% efficacy rate in terminating a routine re-entrant SVT, i.e., AVNRT and AVRT. The drug should be given slowly, unlike adenosine, as a rapid push can lead to unstable hemodynamics. It is contraindicated in infants (< 2 years of age), presence of CHF/prolonged tachycardia, manifest pre-excitation and previous β -blocker therapy. In older children, CCBs are effective and safe.

Overdrive Pacing

Pacing at a rate faster than the tachycardia from the atrium or ventricle is highly effective in terminating re-entrant tachycardias. Overdrive pacing can be done by placing a pacing catheter either in the esophagus or by the transvenous route in the atrium or the ventricle. It acts by rendering tissue ahead of the tachycardia refractory, thus stopping the circus movement responsible for the tachycardia.

DC Cardioversion

It is the treatment of choice for all hemodynamically unstable arrhythmias and for other SVTs not responding to all other techniques/medications. Cardioversion facilities should be available wherever medical termination is being attempted because of the rare occurrence of VF due to enhanced conduction over the accessory pathway.

Biphasic shock is now considered more efficacious and needs less energy for cardioversion. Most SVTs and AFL will respond to as low as 0.25–0.5 Joules/kg whereas VF may need up to 4 Joules/kg, which is the maximal dose permitted for a child. Most tachycardias will respond to DC version though automatic foci may be unresponsive in over 50–70% or recur immediately after converting.

Intravenous Amiodarone

It is useful in a wide variety of arrhythmias. The effect on the AV node usually occurs within 10–15 min, though the Class III effect usually takes 10–12 hours. When given IV the predominant immediate action is β - and Ca channel blockade that successfully reverts most re-entrant tachycardias using the AV node. The IV bolus dose has to be followed by a continuous infusion to maintain the effect. Amiodarone is effective in most automatic tachycardias like EAT, JET and some VTs. IV amiodarone is not innocuous and the threshold for starting it ought to be high; there is a in general serious over-tendency towards using amiodarone as most people believe it is very safe *acutely*. Acute side effects include severe hypotension and cardiogenic shock, acute fulminant liver failure leading to death, acute chest infiltrates needing oxygen and medication, etc.

Figure 10 provides an algorithm for acute management of a regular SVT.

Supraventricular Tachycardia: Chronic Prophylaxis

Once an acute SVT episode has been taken care of, the clinician needs to decide how to prevent future episodes. In general, medication need not be started after the first episode of an SVT unless the SVT was life-threatening or needed DCCV or the child lives in a remote area and cannot reach a hospital in less than 5–6 hours.

When to Start Prophylactic Therapy?

Most SVTs are hemodynamically stable—hemodynamic stability does not mean a normal blood pressure only. One has to see the complete picture implying look for signs of low cardiac output, CHF, labored respiration, a very high ventricular rate etc. Instability generally happens if underlying heart is abnormal, the ventricular rate is too high reaching 270–300 bpm, child was already on β -blockers and someone gave IV CCB, the tachycardia is antidromic and other causes.

Typically, our approach is not to start long-term medication unless there is an ECG documented SVT and the child has had more than one definite sustained episode. Even so, asking a child to take 1 or 2 pills everyday to prevent a self-terminating, hemodynamically stable episode occurring once in 6–12 months may be an overkill. This is important as once drug therapy has

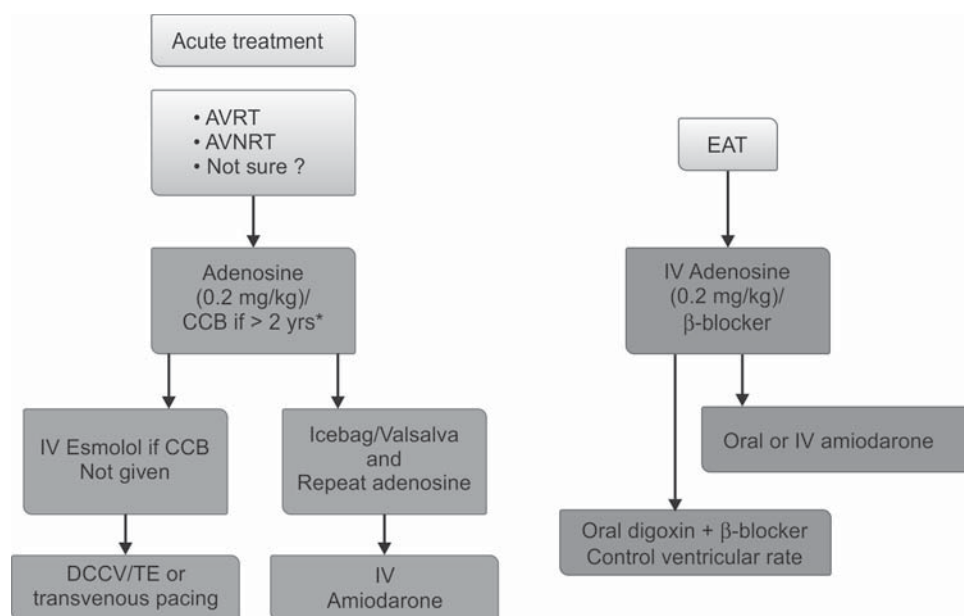


Figure 10 Management algorithm for an ongoing supraventricular tachycardia (SVT). If child is in shock or significant congestive heart failure (CHF), synchronized DC cardioversion (DCCV) with 1–4 J/kg should be done immediately. Re-entrant tachycardias will respond to DCCV but ectopic atrial tachycardia (EAT) would not. IV adenosine is the most favored drug though in older children IV verapamil or diltiazem are effective, safe and much cheaper

*Calcium channel blockers (CCBs) should not be used if child is hemodynamically unstable, < 2 years of age, taking oral β -blockers, known to have Wolff-Parkinson-White (WPW) syndrome or the tachycardia is a wide QRS one. Giving adenosine correctly is very important (see text). Icebag application is also an effective way especially if initial adenosine has failed for some reason

Abbreviations: AVRT, atrioventricular re-entrant tachycardia; EAT, ectopic atrial tachycardia; AVNRT, atrioventricular nodal re-entry tachycardia; TE, transesophageal pacing.

been started it will most likely continue for several years unless tachycardia resolves by itself or a catheter ablation is done. Losing pre-excitation is not at all uncommon in infancy and the same implies for an EAT. Even if pre-excitation persists the child may stop having an SVT as the accessory pathway (AP) may have stopped conducting retrogradely.

If tachycardia in an infant persists beyond 2–3 years it is unlikely to resolve. Uncommonly an AP that has stopped conducting in infancy, may come back at a later age. One needs to remember that AP is essentially a *congenital heart disease* implying it was present at birth—an AP cannot be acquired later in life. Even 70- or 80-year-old can be having an AP that remained undetected as it was concealed or an ECG was never done for the person. One other consideration before starting prophylactic drug therapy is to consider *pill in the pocket* approach that has been used successfully in adults with SVT and AF. It should be remembered that the first termination using this approach has to be done in a monitored hospital setting.

Which Drug to Start?

Once the decision for starting medication has been taken the doctor needs to decide what drug to start. In general, *digoxin*, β -blockers and CCBs are safe drugs with no proarrhythmic potential. The therapeutic range of digoxin is narrow and overdose, hypokalemia, and drug interactions need to be kept in mind and explained to the patient/parents. It is a common belief that children tolerate a higher dose of digoxin up to 10 $\mu\text{g}/\text{kg}$. This is true for children less than 4 years of age and when split into two doses. As far as possible one should not use doses more than 5 $\mu\text{g}/\text{kg}$. Digoxin can be safely combined either with β -blockers or with CCBs.

Medical literature is full of *blanket statements* like digoxin increase mortality when given as a prophylactic agent in WPW

syndrome as it shortens the refractory period of the AP and thus allows antidromic conduction that can take the ventricular rate beyond 300/min or induce VF. This can happen if the patient gets AF or starts conducting antidromically. AF is rare in children and there is no proof that digoxin increases the incidence of antidromic tachycardia *vis a vis* orthodromic tachycardia (generally 90% of SVTs in WPW are orthodromic). To us, the few reports that led to this conclusion of digoxin being harmful in WPW syndrome are not based on rigorous scrutiny. Even so, digoxin should not be first line for WPW syndrome and neither should it be CCBs. Even β -blockers that are in general first line therapy have been proclaimed harmful because it slows AV nodal conduction and hence would increase antidromic tachycardia. This again, is going beyond evidence, experience and *built on theoretical concerns*. We prefer to start with metoprolol in twice daily doses starting at 1 mg/kg/dose. This dose can be increased rapidly based on resting heart rates and blood pressure. If tachycardia recurrences continue despite *adequate* β -blockade one can add digoxin or flecainide/propafenone.

Class Ic drugs like flecainide and propafenone are highly effective drugs and safe when used in normal hearts and in the correct manner. Sotalol, a class III drug is also very useful but can lead to QT prolongation and polymorphic VT (TdP). These drugs should always be started in hospital under ECG monitoring and by physicians experienced in their use. It is important for pediatricians following up such patients to do ECGs regularly (once in 2–3 months) and monitor the QRS/QT intervals. QT prolongation beyond 520 ms, QRS prolongation more than 20–25% or appearance of any conduction defect are to be taken seriously and the drug either stopped or doses readjusted. Milk and milk products alter flecainide absorption and the child should not be given milk/milk products, 2 hours pre- or post-flecainide dose. Flecainide/propafenone should always be used with an AV nodal blocking drug.

Amiodarone should not be used in a routine SVT—neither acutely nor for chronic prophylaxis. We prefer to go for a catheter ablation rather than use amiodarone for more than 6–12 months in any child of any age.

Catheter ablation has revolutionized the management of arrhythmias and in adults it is now used even for arrhythmias like AF, VF, Torsades-de-Pointes, and ischemic VT. Radiofrequency ablation remains the preferred choice with cryoablation having some role in children wherein there is a risk of complete heart block when ablating. The Heart Rhythm Society (HRS) of the US had laid down guidelines for catheter ablation in children in 2002. These guidelines provide a framework that one can build upon. In our view the role of catheter ablation can be understood when one looks at the algorithms and **Table 4**. No cardiac intervention is a zero risk procedure and therefore the referring pediatrician has to be aware of those before deciding for it. **Table 5** summarizes

Table 4 Indications for catheter ablation in children

<i>Definite indications irrespective of age and/or weight</i>
<ul style="list-style-type: none"> Life-threatening tachycardia Tachycardia refractory to medical treatment defined as failed Class Ic and Class III <ul style="list-style-type: none"> Amiodarone may be used for 6 months to an year to tide over Tachycardia associated with significant left ventricular dysfunction High-risk WPW syndrome defined by aborted SCA or <ul style="list-style-type: none"> Recurrent syncope or single syncope plus high-risk markers Manifest pre-excitation associated with significant LV dysfunction Recurrent VT associated with hemodynamic compromise and amenable to catheter ablation Impending congenital heart surgery when vascular or chamber access may be restricted following surgery Parents unable to give medications properly or staying remotely and cannot access medical care quickly Tachycardia not responsive to adenosine/conventional antiarrhythmics and needs DCCV Persistent atrial flutter in a child > 4 years/15 kg
<i>Relative indications: age, weight may need to be factored</i>
<ul style="list-style-type: none"> Recurrent or symptomatic SVT refractory to conventional medical therapy in a child > 4 years/15 kg Adolescent child > 8–10 years with recurrent SVT not wanting to be on medication or getting side effects WPW syndrome in a child > 8–10 years with either high-risk pathway or inability to estimate risk noninvasively Asymptomatic pre-excitation—adolescent child with proven high-risk. Children < 4–5 years do not need to be tested Persistent atrial flutter in a child < 4 years/15 kg SVT with structural heart disease especially Ebsteins anomaly
<i>Notes</i>
<ul style="list-style-type: none"> Nonsustained arrhythmias in the absence of symptoms or ventricular dysfunction should not be taken for catheter ablation First episode of an SVT should not be offered ablation unless child had significant hemodynamic problems and/or was unresponsive to conventional measures Anesthesia often suppresses arrhythmias especially automatic tachycardias. Hence, such patients should be taken up only if they have incessant tachycardia or are big enough to be managed with minimal medications AVNRT, right midseptal and anteroseptal pathways, are close to the AV node. Ablation should be generally deferred till 12–15 years of age unless significant symptoms are present Conventional antiarrhythmic therapy implies digoxin, β-blockers, CCBs <p><i>The abovementioned indications are based on authors experience and not part of any standard guidelines.</i></p>

Abbreviations: SCA, sudden cardiac death; VT, ventricular tachycardia; LV, left ventricle; AVNRT, atrioventricular nodal re-entrant tachycardia; CCBs, calcium channel blockers; DC, direct current cardioversion; SVT, supraventricular tachycardia.

Table 5 Complications/potential harms of catheter ablation in children

<ul style="list-style-type: none"> Vascular access related <ul style="list-style-type: none"> DVT Hematoma, bleeding, local site infection Femoral arterial occlusion if an arterial access was taken and procedure was long, inadequate heparinization, large sheath Lesion related <ul style="list-style-type: none"> AV block, CHB: < 1%, predominantly in AVNRT, pathways close to AV node Acute/chronic coronary injury, phrenic nerve injury Tissue rupture/cardiac perforation at ablation site Pericardial effusion/tamponade Thromboembolism and stroke Increase in lesion size with growth—initial fears not proven Catheter related <ul style="list-style-type: none"> Injury/perforation of coronary sinus Valve damage
<ul style="list-style-type: none"> <i>Radiation related:</i> Depends on procedure time <i>Anesthesia related</i> if GA given <i>Death:</i> Very rare. Can be due to several causes.

Abbreviations: DVT, deep vein thrombosis; CHB, complete heart block; AVNRT, atrioventricular nodal re-entrant tachycardia; GA, general anesthesia.

some of the complications of catheter ablation. Having said that, if needed catheter ablation can be successfully done even in a 3 kg neonate with minimal risk, predominantly of venous thrombosis from where the access is taken. It would not be an overstatement if one says that in today's era no child should die due to a sustained tachyarrhythmia or WPW syndrome in the absence of structural/electrical heart disease. In India catheter ablation in children is currently being done by adult electrophysiologists. In an unpublished informal survey conducted by us around 2 years ago we found that less than twenty children weighing less than 15 kg had an ablation done in India in an year. We chose 15 kg as the cut-off as it has been found that complications are higher in them when compared to children weighing more than 15 kg. A major problem of doing small children is the unavailability of appropriate sized hardware, something pediatricians are well familiar with when they prescribe tablets that need to be given 1/8th or 1/10th. Cryoablation is still not available in India and therefore one has to try and avoid doing ablations close to the native conduction system that could result in a heart block. Electrophysiological tools are getting more and more sophisticated with 3 dimensional mapping systems like the CARTO (Biosense Ltd, Tirat-HaCarmel, Israel) and ENSITE (St Jude Medical Inc., St Paul, MN, US) providing real time signals superimposed on computed tomography (CT) images. These are very useful for ablating complex arrhythmias or reducing radiation.

Flow charts 1 to 4 illustrate algorithms for chronic management of supraventricular tachycardias.

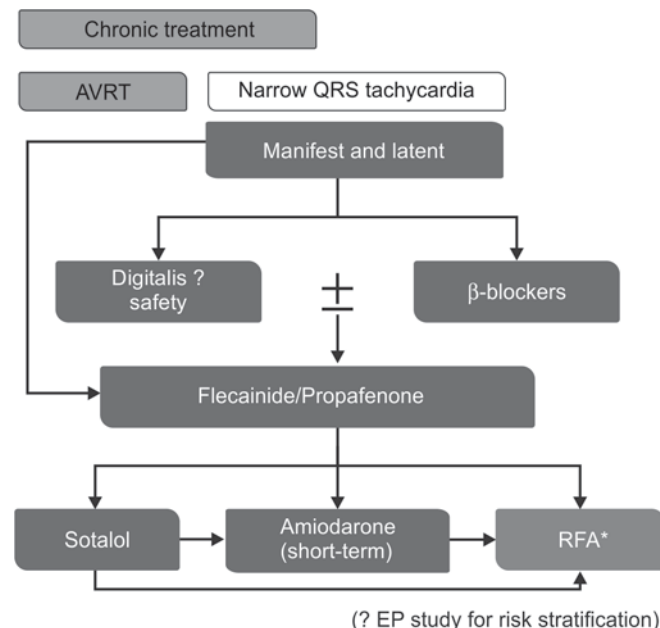
Junctional Ectopic Tachycardia

It usually occurs in a postoperative setting, with 5–10% children developing JET after surgery for congenital heart disease. Congenital JET in the absence of cardiac surgery is very uncommon. JET may be incessant in younger children and lead to TCMP. Presence of AV dissociation in a narrow QRS complex tachycardia is diagnostic of JET.

Treatment

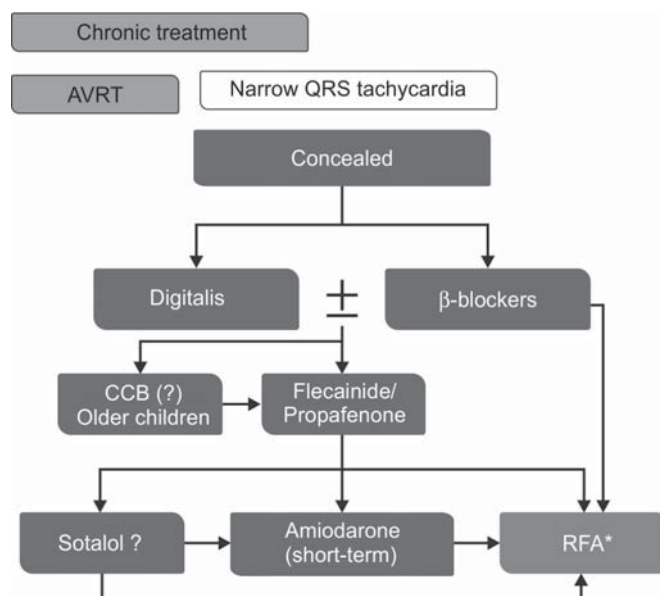
Intravenous infusion of cold saline in addition to surface cooling, to achieve a core temperature of 32–34°C—needs the child to be on a ventilator. IV vasopressors need to be minimized. AV synchrony can be achieved either by restoration of sinus rhythm

Flow chart 1 Drug treatment for preventing re-urrences in Wolff-Parkinson-White (WPW) syndrome. Latent pathways are pathways that have antegrade conduction that manifests only when some intervention is done. These pathways have the same risk as manifest pathways. Use of digitalis in manifest pathways is questionable (see text for discussion). Similarly use of sotalol for a benign arrhythmia like supraventricular tachycardia (SVT) may not be a good choice. Risk stratification by an electrophysiologic (EP) study is carried out by several groups in the US and RFA done for high-risk pathways even in young children



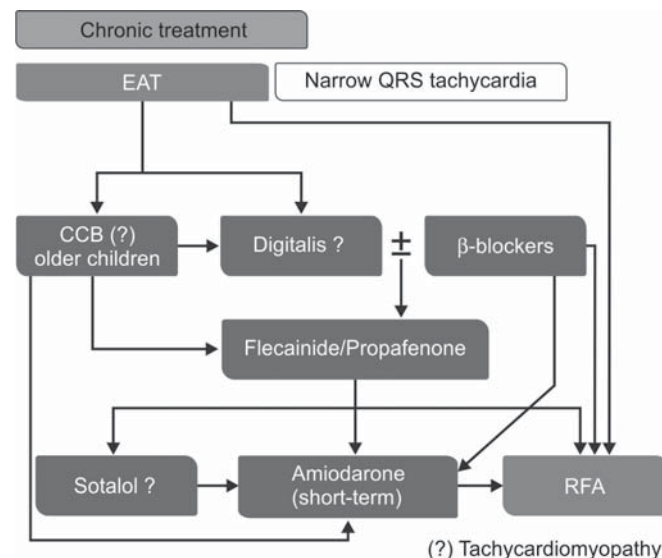
Abbreviation: AVRT, atrioventricular re-entrant tachycardia.

Flow chart 2 Algorithm for concealed APs. Since they do not have antegrade conduction the risk of sudden cardiac death (SCD) is much lower than Wolff-Parkinson-White (WPW) syndrome. Hence, both digitalis and calcium channel blockers (CCBs) can be used safely. In refractory supraventricular tachycardias (SVTs) combination therapies like flecainide with sotalol or amiodarone have been used by some. We feel RFA should be done rather than use relatively dangerous antiarrhythmics



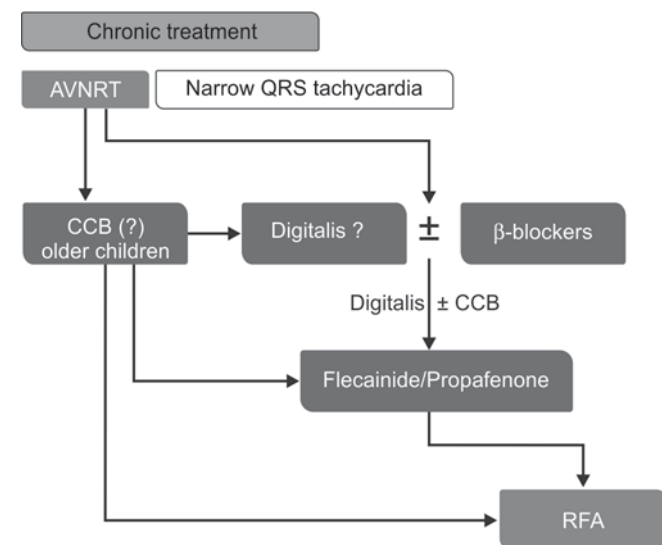
Abbreviation: AVRT, atrioventricular re-entrant tachycardia.

Flow chart 3 Therapy for ectopic atrial tachycardias can be started in the same way. However, most ectopic atrial tachycardias (EATs) do not terminate with this combination, but ventricular rate slowing maybe a reasonable endpoint. Amiodarone is a useful drug to restore sinus rhythm especially if there is severe left ventricular dysfunction which excludes use of Class Ic drugs. Presence of tachycardiomyopathy is an indication for early RFA or one could use amiodarone for a few months, let the LV function improve and then use safer drugs or ablate



Abbreviation: EAT, ectopic atrial tachycardia.

Flow chart 4 Atrioventricular nodal re-entry tachycardia (AVNRT) is an uncommon arrhythmia in small children. It can be easily managed by drugs like digoxin, β-blockers or calcium channel blockers (CCBs) or their combination. Radiofrequency (RF) ablation should not be attempted unless it is refractory or the child reaches adulthood. Risk of complete heart block is < 1 in 1,000 in experienced centers in adults. In children it may not be that low as the triangle of Koch is smaller. Cryoablation maybe preferable as it is safer than RFA



or atrial pacing. IV amiodarone in general reverts the tachycardia. Prior to reversion it may lead to a decrease in the rate and allow atrial capture with dual chamber pacing. It can be combined with flecainide in refractory JET. Oral amiodarone can be given to a child with stable hemodynamics and 2-3 days postprocedure.

Radiofrequency ablation has been attempted but has a high risk of complete heart block (CHB) and should be attempted only if tachycardia is life-threatening not responding to conventional means.

VENTRICULAR TACHYCARDIA AND VENTRICULAR FIBRILLATION

Ventricular tachycardia classically presents as a wide QRS tachycardia. QRS width is dependent on the age of the child and should be interpreted accordingly. In neonates a QRS width more than 80 ms is clearly abnormal. Widening of QRS may be very subtle and missed. The presence of AV dissociation in the presence of fast ventricular rate should suggest VT. It is important to note that Vs should be more than As as AV dissociation can be seen in complete heart block too.

Types

Monomorphic VT in the presence of a normal underlying heart can be stable and therefore hemodynamic instability should not be considered as evidence for VT. A sustained VT can result in hemodynamic compromise and VF. *Polymorphic VT* is generally rapid and leads to hemodynamic compromise. VT can be seen in very diverse circumstances. *Fascicular VT*, also called as idiopathic LVT can be seen with a normal heart. A similar VT morphology with a slightly wider QRS (complete LBBB) can also be using the fascicles in the presence of LV dysfunction, that is called as a *bundle branch re-entrant VT*.

Diseases like LQTS that were earlier called as primary electrical diseases of the heart are now grouped under the umbrella of *Channelopathies* as these occur due to abnormalities in the ion channels of the heart. Structurally these hearts are completely normal. Most of these diseases are inherited and are associated with sudden cardiac death. Genetic screening/testing has therefore become a very important tool in management of these diseases and SCD.

Etiology

The common causes of VT are as follows:

- Myocarditis, myocardial ischemia or infarction.
- Cardiomyopathies—dilated and hypertrophied types and in noncompaction of left ventricle.
- Cardiac tumors like rhabdomyomas, myocardial hamartomas (Purkinje cell tumors), fibromas and histiocytic tumors.
- Several congenital heart diseases are prone to develop ventricular arrhythmias either as such or due to the ventricular dysfunction they produce. Almost one-third of patients of Eisenmenger syndrome die suddenly, presumably due to a ventricular arrhythmia. Patients of TOF repair gradually develop RV enlargement due to the pulmonic regurgitation that most of them are left with. Such patients often develop VT that is re-entrant going around the VSD patch or using the RVOT.
- Channelopathies like LQTS, Brugada syndrome, catecholaminergic VT, short QT syndrome and others. Ion channel problems are also seen in arrhythmogenic right ventricular dysplasia (ARVD) in which RV myocardial thinning occurs with replacement by fibrous tissue and fat. This disease is also labeled as a cardiomyopathy as right ventricular dilatation and dysfunction are an integral part of it.
- Drug toxicity, e.g., digitalis, catecholamines, theophyllines, etc. Most antiarrhythmics are themselves proarrhythmic as they alter channel conduction.
- Idiopathic (fascicular VT) and right ventricular/left ventricular outflow VT—both occur on an underlying normal heart.
- Electrolyte disturbances like hypokalemia, hypocalcemia can also lead to VT.

Conditions Causing Ventricular Tachycardia/ Ventricular Fibrillation

Long QT Syndrome

QT prolongation can lead to a polymorphic VT called as Torsades-de-Pointes. QT may be prolonged either as a genetic defect or it may be *acquired* with common offenders being drugs, hypokalemia, hypocalcemia, intracranial hypertension, etc. Antiarrhythmics (quinidine, sotalol, amiodarone), antihistaminics like terfenadine, antibiotics like quinolones, motility agents like cisapride and several other drugs have been associated with QT prolongation with some of them being discontinued because of this.

The *congenital variety* is typically adrenergic dependent and has several subtypes based on the exact genetic defect and the channel affected. In LQT1, the most common variant of LQTS, patients typically get a VT during exercise while in LQT2 events are triggered by startle or auditory stimuli. LQT3 is one of the more malignant forms wherein events occur during sleep or inactivity. Diagnosis of LQTS is easy when the ECG shows the same or when a family member has already been diagnosed as having the problem. However, these patients may not show a long QT all the time and even 24 hours Holter recordings may fail to pick it up. Patients presenting with syncope or sudden cardiac arrest as the only manifestation may need intensive evaluation before one hits the diagnosis. An exercise test can be very useful in provoking the QT abnormality and should be part and parcel of evaluation of syncope. It is not uncommon to find LQT in patients being treated for refractory seizures. Diagnostic criteria for LQT exist but broadly an unequivocal diagnosis of LQT is made if it is more than 480 ms. Lesser degrees or prolongation will need supportive evidence. It is possible that patients getting torsades due to drugs actually have a subclinical genetic defect that gets provoked. Typically the drug induced torsades is pause dependent wherein an early coupled ectopic falls on the T wave that occurs late because of the preceding pause.

Management depends of the variant type. In general, high dose β -blockers in combination with atrial pacing form the mainstay of treatment. Left cardiac sympathetic denervation and implantable cardioverter defibrillator (ICD) implantation may be done in carefully selected patients. Management of a drug induced torsades in the emergency room maybe stabilized by isoprenaline infusion, pacing and IV magnesium. It may seem paradoxical that one uses isoprenaline and β -blockers for the same disease. Acutely if pauses are seen, isoprenaline is useful. β -blockers help in prophylaxis for recurrences.

Catecholaminergic Polymorphic Ventricular Tachycardia

This is characterized by a bidirectional or a polymorphic VT that is associated with a structurally normal heart and is characteristically precipitated with exercise and emotional stress. Management of CPVT consists of β -blockers, with ICD implantation for those experiencing cardiac arrest, sustained VT or syncope despite maximal therapy.

Idiopathic Left Ventricular Tachycardia

This is the only VT that is relatively *narrow complex* (**Fig. 11**). QRS complex is *narrow*, typically 100 ms, as the impulse travels through the fascicles, which is a rapid conductor. It is the only VT that is sensitive to verapamil. The most common variety arises from the left posterior fascicle and thus the QRS shows an incomplete right bundle branch block (RBBB) with left axis. Given that RBBB should have a right axis, this ECG pattern is classical.

Treatment Idiopathic left ventricular tachycardia (ILVT) is mostly stable and therefore gives adequate time to diagnose and treat.

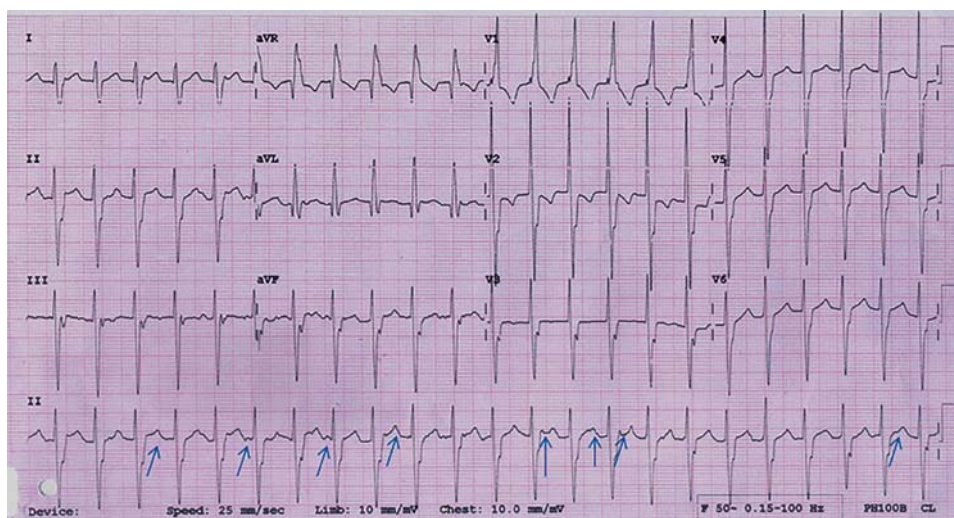


Figure 11 Narrow QRS tachycardia at approximately 140 bpm. The QRS duration is < 120 ms but wider than what a usual QRS in supraventricular tachycardias (SVTs). There is an incomplete RBBB with left axis that is classical of fascicular ventricular tachycardia (VT). The arrows point to the P waves that distort the shape of ST-T segment as they are dissociated from the ventricle (VA dissociation). The QRS onset is very sharp that also points to its fascicular origin as myocardial VTs show a gradual onset because of the slow conduction

In general CCB should not be given for a VT and thus any wide QRS tachycardia. Acutely, lidocaine (1.0 mg/kg/dose over 1–2 min) may be given followed by lidocaine infusion. If diagnosis is certain, IV verapamil or diltiazem can be given. IV Amiodarone is also effective but is rarely needed. DCCV can be done if all measures fail. RF ablation is treatment of choice in older children and adults.

BRADYARRHYTHMIAS

Bradyarrhythmia may occur due to either a defect in impulse formation or conduction.

- Disorders of impulse formation
 - Sick sinus syndrome (sinus pauses, sinus arrest)
 - Nonspecific, scar-like degeneration of the heart's conduction system, often age-related (not common in children)
 - Familial, hypothyroidism, drugs
 - Congenital heart diseases associated with isomerism and situs ambiguus
 - Postoperative, e.g., following a Glenn shunt, Senning operation.
- Disorders of impulse conduction
 - Sinus node conduction abnormalities
 - AV blocks: First degree, second degree and complete heart block. It maybe congenital, postoperative, or associated with congenital heart diseases like corrected transposition of great arteries (cTGA), AV septal defects
 - Diphtheritic myocarditis, Lyme's disease, viral myocarditis
 - Hyperkalemia
 - Drugs like CCB, β -blockers, digoxin, tricyclic antidepressants can also lead to blocks
 - Poisoning with aluminum phosphide, yellow oleander.

ATRIOVENTRICULAR BLOCK

A disorder of conduction of impulse from atrium to ventricles is due to AV block which is classified according to the severity of conduction abnormality. In mild cases, only prolongation of PR interval occurs (first degree AV block), in more severe cases, some of the atrial impulses are not conducted into the ventricles (second

degree AV block) and in most severe cases, none of the atrial impulses are conducted to the ventricles (complete AV block).

COMPLETE HEART BLOCK

Complete heart block is the most common bradycardia (after sinus bradycardia) in a child (**Fig. 12**). In general, the heart is structurally normal, though it is well known to occur in cTGA. Although literature suggests that 50% of mothers with children having congenital CHB (CCHB) will have manifest connective tissue disease especially systemic lupus erythematosus (SLE) our experience is not the same. We have rarely seen manifest SLE in the mothers but more than 90% have positive anti-Ro and anti-La antibodies. Conversely, firstborn of mothers with SLE or positive antibodies have an incidence of CHB of 1–2%. The risk of recurrence in a subsequent child increases to 10–16%. The CHB usually occurs in the second or third trimester and may be preventable by immunosuppressants. Once CHB has occurred, it does not resolve, though the ventricular rate maybe increased by sympathomimetics.

The newborn with CCHB may have varied manifestations but is often asymptomatic. This primarily depends on the origin and stability of the escape rhythm that mostly comes from AV junctions. With structural heart disease the child may have significant cardiomegaly and CHF. Symptoms like CHF, seizures due to intermittent asystole or fast polymorphic ventricular tachycardia, failure to thrive are obvious indications for pacing. The decision to pace becomes more difficult when the child is asymptomatic. Over 75% of children with asymptomatic CCHB would eventually need a pacemaker by the age of 20.

Indications for pacing in asymptomatic congenital complete heart block are summarized in **Table 6**. Pacemakers in children can be implanted epicardially or endocardially depending on the weight of the child, access site, risk of a systemic embolization etc. Children with hemodynamically significant VT may need ICDs. Devices like pacemaker and ICD in children are a highly specialized area but give a near normal life to the child. It is important for pediatricians to make the child feel normal and allow them all activities. In general, current pacemaker batteries are good enough to last for at least 10 years. However, this is a function of the current needed, paced heart rates, duration of pacing, single or double

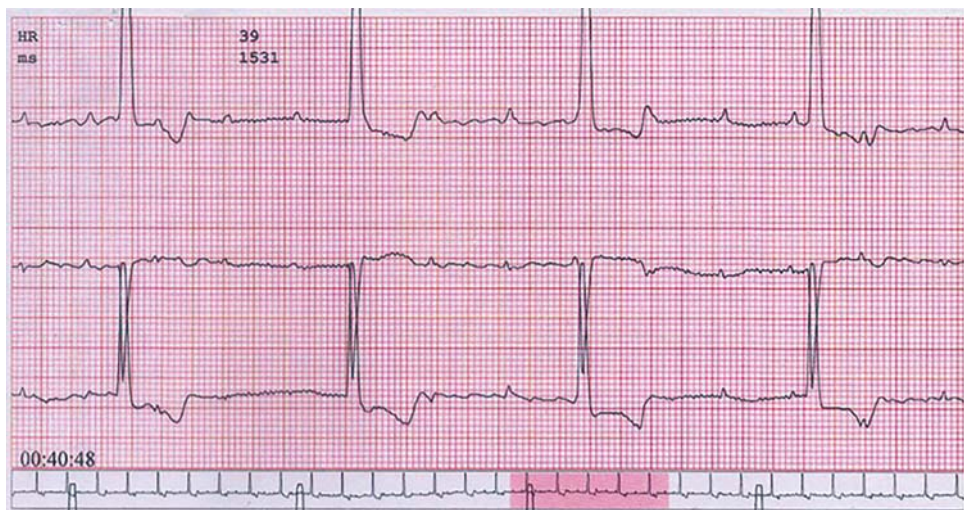


Figure 12 Three-channel Holter recording of a 13-month-old child with complete heart block (CHB). Note the P waves are marching through the QRS complexes. To diagnose CHB the atrial rate should be faster than ventricular rate, the PR interval will change constantly and the ventricular rate will be constant. Since ventricle does not get any input, some part of the junction or the ventricle starts to fire to keep the heart going. Lower the origin of the escape rhythm, lower is its rate and broader is the QRS. In this child the maximum QRS duration is 120 ms which is way longer than the normal range at this age of 33–78 ms. This implies the rhythm is coming from the ventricle or the bundles and one cannot rely on them. This is a definite indication for a permanent pacemaker implantation

Table 6 Indications for pacing in asymptomatic congenital complete heart block (CCHB)

• QRS of the junctional escape rhythm is wide for the age of the child
• Mean daytime awake ventricular rate < 50/min in infants and children, < 55/min in neonates and < 65/min in the presence of structural heart disease. Sleep rates < 30/min may also be considered as an indication for pacing
• Cardiomegaly not attributable to other reasons
• Frequent ventricular ectopy, NSVT and presence of short coupled VPBs
• Poor chronotropy
• CHF
• Prolonged QTc > 480 ms or absolute QT > 600 ms

Abbreviations: CHF, congestive heart failure; NSVT, nonsustained ventricular tachycardia; VPBs, ventricular premature beats.

chamber, etc. In the current era, no child should die because of inability to give a pacemaker.

SUDDEN CARDIAC DEATH/SUDDEN CARDIAC ARREST IN CHILDREN

Sudden cardiac death or sudden cardiac arrest (SCA) is defined as cardiac arrest occurring within an hour of onset of symptoms in a person with known or unknown heart disease—the timing and mode of death should be unexpected. The term SCD has a limitation as a large number of these patients (predominantly in the developed world) now survive the immediate event by aggressive and efficient resuscitation. This led to a paradoxical term called as SCD survivors and therefore SCA is a preferred term now. There are several causes of SCA that are listed in **Table 7**.

CONCLUSION

We have tried to give a broad overview of cardiac dysrhythmias in children. It is important for pediatricians to understand the

genesis and mechanism of arrhythmias. It is equally important not only to recognize the arrhythmia going on but try and find the type/mechanism. Thus, when confronted with a narrow QRS tachycardia one should be able to diagnose whether it is sinus tachycardia, AVRT, EAT or atrial flutter/fibrillation. This is important because it determines the immediate treatment and the long-term management. Catheter ablation has provided a *cure* for several of these arrhythmias, unlike most other chronic diseases that can be only controlled on drugs. Cardiac devices are getting more and more sophisticated, smaller in size and affordable. More and more children will need such devices in the future as results and numbers of surgical procedures for congenital heart disease increase. India and many other developing nations face a severe shortage of experts in managing these children and we hope this chapter can inspire some of you to choose this specialty.

Table 7 Cardiac disorders predisposing to sudden cardiac death (SCD)

Structural/functional
• Hypertrophic cardiomyopathy
• Coronary artery anomalies
• Dilated cardiomyopathy or restrictive cardiomyopathy
• Myocarditis
• Left ventricular outflow tract obstruction
• Arrhythmogenic right ventricular cardiomyopathy
• Postoperative congenital heart disease
Electrical
• Long QT syndrome
• Wolff-Parkinson-White syndrome
• Brugada syndrome
• Catecholaminergic polymorphic ventricular tachycardia
• Short QT syndrome
• Complete heart block
Other
• Drugs and stimulants; some prescription medications
• Primary pulmonary hypertension

IN A NUTSHELL

1. Cardiac arrhythmias (preferably called as dysrhythmias) are omnipresent and pediatricians of today have to improve upon their ECG reading, interpretation and management.
2. In general nonsustained arrhythmias, even ventricular arrhythmias to a certain extent are benign, if the underlying heart is normal, structurally and electrically.
3. Arrhythmias should be treated only if, they are causing symptoms or leading to hemodynamic problems such as hypotension, congestive heart failure, syncope, etc.
4. Tachyarrhythmias are currently divided into two major groups that are supraventricular and ventricular tachyarrhythmias. Most tachyarrhythmias occur due to re-entry.
5. A 12-lead ECG, preferably in rhythm format (12 × 1), should always be done when the patient comes with a sustained arrhythmia. Every effort should be made to record the ECG while giving intravenous adenosine.
6. Atrioventricular re-entrant tachycardia (AVRT) due to a manifest or concealed pathway is the most common cause of sustained cardiac arrhythmias in infants and children. WPW syndrome, i.e., manifest pre-excitation with symptoms can very occasionally lead to sudden cardiac death (SCD) at the rate 0.05%/year.
7. DC cardioversion (DCCV) should always be ready when treating any sustained arrhythmia. Even intravenous adenosine can lead to ventricular fibrillation in an occasional patient of WPW syndrome.
8. Sustained tachyarrhythmias may lead to a reversible *dilated cardiomyopathy like picture*, that normalizes once the tachycardia is taken care of. Manifest pre-excitation by itself can lead to left ventricular dysfunction due to the dys-synchrony caused by it.
9. Prophylactic drug therapy for most tachyarrhythmias should be used only for symptomatic patients having frequent sustained arrhythmias. It is not necessary to give pills to a child everyday to prevent an SVT that occurs once or twice a year.
10. Amiodarone oral and intravenous is a toxic drug that should not be used or, if unavoidable, then given for as short a time as possible. Oral amiodarone should not be used for a benign SVT in a normal heart.
11. Flecainide, propafenone and sotalol are highly effective drugs in preventing several arrhythmias. However, these should only be used by doctors who are familiar with its use and in patients whose ECG can be monitored on a regular basis.
12. Catheter ablation has revolutionized the management of tachyarrhythmias with very high success rates, typically over 95% in most SVTs and VTs with normal hearts. It has been used successfully even in neonates, if indicated.
13. Diagnostic electrophysiological studies have a limited role in the current era especially for bradycardias and blocks.
14. Sudden cardiac death/sudden cardiac arrest (SCD or SCA) is not an uncommon event in infants and children.
15. Primary electrical diseases of the heart such as long QT syndrome, Brugada syndrome, CPVT, short QT syndrome, Early repolarization syndrome, idiopathic VF, etc., are now called as *channelopathies* as all these defects are linked to the ion channels in the heart. They are frequently missed and one important rule is to get an ECG done for every patient having frequent *seizures*. Family history of sudden death should always be probed with due diligence in children with syncope, seizures.

MORE ON THIS TOPIC

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Chapter 40.38

Cardiac Emergencies

Umesh Dyamenahalli

Though cardiovascular emergencies of life-threatening nature are infrequent in children, adequate awareness, high index of suspicion and preparedness for arriving at precise early diagnosis and instituting appropriate and timely management are necessary to minimize morbidity and the mortality. Delay in recognition and optimal management can lead to devastating outcomes. With evolution and timely improved interventions and perioperative care, the survival of these patients has improved remarkably. Newborns, infants and children with heart disease may present to emergency facilities as undiagnosed congenital heart disease (CHD) with complications, after palliative surgical procedures, after definitive repair, or with acquired cardiovascular disorders.

Pediatric cardiac emergencies (**Table 1**) are due to variety of pathology including imminently life-threatening CHDs, arrhythmias, infections, inflammatory conditions, familial conditions and trauma. Other pediatric cardiac emergencies presenting as chest pain, syncope and near missed cardiac deaths are beyond the purview of this chapter.

EMERGENCY EVALUATION OF NEONATES AND INFANTS WITH SUSPECTED CONGENITAL HEART DISEASE

Patients with significant CHD present in the first few days and weeks after birth with signs and symptoms of cyanosis, shock, congestive heart failure or significant murmur. It is not uncommon to find newborns with ductal dependent lesions appearing to be normal

on routine newborn examination after birth in the first few days to be sent home but only to return with serious and life-threatening clinical findings that require immediate intervention. Urgent assessment, initial stabilization and expeditious consultation is essential when severe, potentially lethal CHD is suspected in critically ill neonates who present with shock, cyanosis, or pulmonary edema.

Clinical Evaluation

Evaluation of a neonate or an infant with suspected CHD includes thorough history and physical examination which must essentially include looking for cyanosis and careful checking of the quality of arm and leg pulses along with four limb blood pressure measurements, both of which are considered vital for early detection of critical or severe CHD. If there is diminished or absent peripheral pulses and perceptible difference in arm and leg pulses, ductal dependent systemic flow lesions such as critical aortic stenosis, coarctation of aorta (CoA), interrupted aortic arch and hypoplastic left heart syndrome must be suspected. Chest radiographs, electrocardiogram (ECG) and if indicated *hyperoxia test* and echocardiograms are an extension of initial assessment. Pulse oximetry is helpful to detect mild desaturation in patients with ductal-dependent lesions, as mild desaturation may be difficult to appreciate visually.

Neonatal Cardiac Emergencies due to Ductal Dependent Congenital Heart Disease

It is important to realize that any infant less than or equal to 6 weeks who presents in shock or profoundly cyanotic might be secondary to closure of the ductus arteriosus in conjunction with a right- or left-sided obstructive cardiac lesion. The two most important presentations of life-threatening neonatal cardiac emergencies are: (1) onset of acute hypoxemia within or after 24 hours of birth manifest clinically as worsening cyanosis, and if untreated

Table 1 Cardiac emergencies based on age and etiology

Structural congenital heart diseases (CHDs)	
Neonates: (A) Ductal dependent (Dd) CHDs	
• Duct dependent pulmonary blood flow (presents with severe cyanosis, acidosis, reduced feeding and motor activities)	TOF, PAtr with VSD, PAtr with intact septum, critical PS, TA, Ebstein anomaly of TV, heterotaxy (most often)
• Duct dependent systemic blood flow (presents with shock, feeble pulse, peripheral and/or minimal central cyanosis)	Neonatal CoA, critical AS, HLHS, interrupted aortic arch, heterotaxy (less common)
Neonates: (B) Nonduct dependent cyanotic CHDs	
• Cyanosis often with features of heart failure	Truncus Art., TAPVR, d-TGA (D-TGA is not duct dependent lesion, however, PDA does improve mixing at atrial level by increasing pulmonary venous return, especially with an intact ventricular septum)
• Severe cyanosis and respiratory distress	Obstructed type of TAPVR, pulmonary hypertension
• Neonatal cardiac dysfunction (presenting as CHF)	Dilated cardiomyopathy/myocarditis, severe hypertrophic cardiomyopathy, rarely ALCAPA, complete congenital heart block
• Fetal and neonatal arrhythmias	SVT (re-entry narrow complex tachycardia), VT, complete congenital heart block, atrial flutter
Cardiac emergencies in postneonatal period, infancy and childhood	
Those presenting with CHF	Large left to right shunt—large VSD, PDA; large common mixing lesions—truncus arteriosus and ALCAPA
Pericardial effusion	
Cardiac conditions associated with other congenital anomalies	
Tetralogy of Fallot with hypercyanotic spells	
Postoperative conditions—functional and structural abnormalities along with patient specific problems	

Abbreviations: TOF, tetralogy of Fallot; PAtr, pulmonary atresia; PS, pulmonary stenosis; TA, tricuspid atresia; Truncus Art, truncus arteriosus; TAPVR, total anomalous pulmonary venous return; d-TGA, d-transposition of the great arteries; CHF, congestive heart failure; CoA, coarctation of aorta; AS, aortic stenosis; ALCAPA, anomalous origin of the left coronary artery from the pulmonary artery; VSD, ventricular septal defect; PDA, patent ductus arteriosus; HLHS, hypoplastic left heart syndrome.

develops acidosis (**Table 1-neonate A**) and (2) shock such as state with feeble pulses, poor peripheral circulation, acidosis and decreased activity and responsiveness (**Table 1-neonate B**).

Newborn with Cyanosis and Acidosis

The first clinical scenario (**Table 1-neonate A**) indicates the possibility of a CHD with right ventricular outflow tract obstructive lesions (extreme tetralogy, critical pulmonary stenosis or atresia, tricuspid atresia, d-transposition of great arteries with inadequate mixing) where presence of a patent ductus arteriosus (PDA) is crucial to maintain better pulmonary blood flow and hence improved arterial oxygen saturation sufficient to keep the neonate in stable condition and alive. These conditions are hence called ductus dependent pulmonary blood flow conditions. The neonate becomes acutely symptomatic when the ductus arteriosus closes after birth with the development of the earlier symptomatology.

The *primary life-saving resuscitative step* in such a scenario is to reopen the ductus arteriosus or prevent its further closure by giving intravenous (IV) infusion of prostaglandin E1 (PGE1) (starting dose: 0.05–0.1 µg/kg/min, may go up to 0.2 µg/kg/min, in the absence of satisfactory response in saturation and acid-base parameters, and cautiously wean the dose to the effective minimum maintenance dose of 0.01 µg/kg/min). The use of PGE1 in an effort to reopen ductus is acceptable in the first 30 days of life. Other important resuscitative steps are listed as follows:

1. Oxygen administration so as to keep the saturations between 75% and 85%, if necessary intubation and ventilation.
2. Improving preload by expansion of blood volume using either 10 mL/kg of 0.9% saline or 5% albumin IV bolus with repeated boluses till liver edge becomes palpable.
3. Correcting acidosis and maintaining the acid-base equilibrium. If necessary IV sodium bicarbonate (1 mEq/kg of 4.2 5% solution). If the pH is more than 7.25, there is no need correct the acidosis rapidly by giving bicarbonate—please see oxygen dissociation in acidic pH.
4. Correcting other possible metabolic derangements such as hypoglycemia, hypocalcemia.
5. Empiric antibiotics, if sepsis is suspected.
6. Judicious use of inotropes/vasopressors, only when indicated to maintain adequate systemic perfusion.
7. Making concurrent efforts to evaluate the neonate and diagnose the underlying structural CHD with the help of echocardiography (Echo) performed by pediatric cardiologist and cardiac centers for appropriate surgical intervention.
8. Intubation with assisted ventilation under sedation with or without paralysis to improve oxygenation and limit metabolic demands.

Newborn with Heart Failure

The second clinical scenario (**Table 1-neonate B**) indicates the possibility of a CHD with left-sided outflow tract obstructive lesions, such as hypoplastic left heart syndrome (HLHS), critical mitral or aortic valve stenosis or atresia, CoA, interrupted aortic arch, where presence of a PDA is crucial to maintain adequate systemic arterial circulation to keep the neonate alive. These conditions are therefore called ductus dependent systemic blood flow conditions. The neonate becomes acutely symptomatic when the ductus arteriosus closes after birth with the development of the earlier symptomatology.

The life-saving resuscitative steps mentioned earlier are the same starting with immediate admission into neonatal intensive care unit (NICU) set-up with prostaglandin E1 infusions, volume resuscitation with frequent IV aliquots of 5–10 mL of 0.9% normal saline or 5% albumin, if readily available, and oxygen to maintain saturation around 75–85% and all the other steps enumerated

earlier. Long-term survival is possible, if these steps are followed efficiently till the stabilized neonate is safely entrusted to the care of safe surgical experts. Here, it is very important improve cardiac output and avoid measures which might increase pulmonary flow.

Functional Single Ventricle

A wide anatomic variety of lesions are usually associated with hypoplasia or atresia of atrioventricular, semilunar valves or outlets sharing similar physiology of complete mixing of the systemic and pulmonary venous blood. A few others with good sized valves are unable to achieve biventricular circulations because of associated malattachment, or straddling of the valves. On an emergency basis, it is imperative and urgent to assess and understand the following parameters: (1) Is the underlying CHD a ductal dependent condition; (2) Is cardiac output adequate not to endanger survival of the neonate; and (3) Presence of evidence for specific known syndromes and/or involvement of other organs. In addition precise understanding of the unique physiology of patients born with complex CHDs with single functioning ventricle is required to effective management.

Some of the examples of CHDs with single functioning ventricle physiology are: (1) hypoplastic left heart syndrome, (2) tricuspid atresia, (3) unbalanced atrioventricular canal defects, (4) double outlet right ventricles, and (5) double inlet ventricles. Some of these patients may have adequate pulmonary and systemic flow, while in others the pulmonary or systemic blood flow depends on the patency of the ductus arteriosus. The common finding among these defects is that the heart has only one effective functioning ventricle taking extra workload (pressure and volume overload) in pumping blood to both the body (systemic circulation) and lungs (pulmonary circulation). Effective initial management is vital to minimize other organ dysfunction and prevent cardiorespiratory arrest and to improve survival outcomes.

CRITICAL CONGENITAL CARDIAC DISEASES

Most of these conditions have been already discussed in detail in respective chapters. Here, only the emergency management part is described.

Coarctation of Aorta (Critical)

Newborns with critical CoA invariably present with the spectrum of profound shock, metabolic acidosis and multiple organ dysfunction. The pulse difference between upper and lower limbs may not be present, if there is myocardial dysfunction. Differential cyanosis may be present, because of right to left shunt across PDA in presence of pulmonary hypertension. Neonates and infants with CoA can present with progressive congestive heart failure, usually before 4 months of age. Administration of prostaglandin E1 infusion in newborns and other life-saving supportive therapy is necessary; followed by referral for appropriate assessment and surgical intervention.

Hypoplastic Left Heart Syndrome

Hypoplastic left heart syndrome is characterized by poor peripheral perfusion with cyanosis, pallor, and difficult to feel peripheral pulses (unless there is PDA and balanced systemic and pulmonary flow). Systemic saturations can be in the range of 70s–80s. Echo is essential for the diagnosis. Prostaglandin E1 infusion (0.01–0.1 µg/kg/min) to preserve the patency of the ductus arteriosus, and to maintain adequate systemic circulation is the main stay of initial management. It is essential to avoid measures that could decrease pulmonary vascular resistance and increase pulmonary blood flow [i.e., high fraction of inspired oxygen (FiO₂), and hyperventilation]. This is to be followed by appropriate surgery.

Tetralogy of Fallot

Neonates with tetralogy of Fallot (TOF) having pulmonary atresia present with severe cyanosis and are ductus dependent for their pulmonary blood flow to minimize severe cyanosis. The immediate management will be directed to keep the ductus open. In infants and children, the most common emergency is hypercyanotic spell (Tet spells). These occur in infants and children with unrepaired TOF and other cardiac defects with ventricular septal defect and narrow pulmonary outflow tract (tricuspid atresia and normally related great arteries). Children with episodes of self-limiting cyanotic spell should be considered for early surgical intervention. Tet spells are a medical emergency deserving emergency management.

Management of Cyanotic Spell

These spells are usually seen between the ages of 1 month and 12 months, in the morning, after waking from sleep; defecation, agitation, dehydration, crying and invasive procedures without proper sedation are usual precipitating factors. The spell is manifested by increase in rate and depth of respiration (hyperpnea) and increasing cyanosis; it may progress to limpness and loss of consciousness. Examination reveals an agitated and cyanotic infant and a previously heard cardiac murmur of right ventricular outflow obstruction is either absent or markedly decreased in intensity during the spell. The mechanism causing the spells is not completely understood; it is likely due to spasm of the right ventricular outflow tract (infundibulum) resulting in markedly decreased pulmonary blood flow along with right-to-left shunting across the ventricular septal defect (VSD). Infundibular spasm may be precipitated by acute increase in endogenous catecholamines. Management is outlined in **Table 2**.

D-Transposition of the Great Arteries

D-Transposition of the great arteries (TGA), a lethal and relatively frequent malformation, accounting for upto 5–7% of critical CHD. These patients usually presents with cyanosis with the saturations in 60s–70s within 2 days of life. Degree of desaturation depends on intracardiac mixing, effective pulmonary flow and cardiac output. They breath comfortable but tachypneic. Supplemental oxygen does not improve saturation. Prostaglandin improve saturations by

increasing pulmonary flow, therefore increased pulmonary venous return results in better intracardiac mixing via patent foramen ovale or atrial septal defect (ASD). Usually, these newborns have normal pulses and blood pressures. If there is no intracardiac mixing (shunt) without any ASD or VSD severe cyanosis persists with severe hypotension despite prostaglandin infusion and PDA. These neonates will require balloon atrial septostomy to facilitate intracardiac mixing at atrial level.

Obstructive Total Anomalous Pulmonary Venous Return

Pulmonary veins drain anomalously into a systemic venous structure rather than directly into left atrium. There is common collecting pulmonary venous confluence. Obstructive type of total anomalous pulmonary venous return (TAPVC) is symptomatic soon after birth with severe respiratory distress and cyanosis, less commonly with signs of low cardiac output. Cardiac examination shows prominent right ventricular impulses and loud P₂, with or without a murmur—either pulmonary flow ejection murmur or tricuspid regurgitant holosystolic murmur. Liver usually is enlarged. Echo is diagnostic. Supportive therapy, likely need intubation and ventilation and right heart support. Prostaglandin infusion is usually not necessary.

Ebstein Anomaly

It can be challenging to treat severe Ebstein's anomaly with severe tricuspid regurgitation. Initially, prostaglandin use may be necessary to maintain the ductal patency, however, one needs to take the measures to lower the pulmonary vascular resistance (supplemental O₂, minimize lung atelectasis, if necessary nitric oxide may be needed).

HEART FAILURE AS EMERGENCY

Details of heart failure and its management have been already discussed in detail in the previous chapter. Congestive heart failure may occur secondary to structural CHDs, and other genetic, metabolic, nutritional, electrophysiological and infective causes of myocardial dysfunction. Causes of heart failure according to the age at presentation are listed in **Table 3**. Drugs used for treating heart failure are summarized in **Table 4**.

Table 2 Management of hypercyanotic or Tet spells

<i>Objectives of therapy</i>	
To improve pulmonary flow and to minimize alveolar hypoxemia; to increase venous return, to decrease catecholamine surge	
<i>Management steps</i>	
1.	Supplemental oxygen (facemask) (temporarily discontinued, if baby gets more agitated and restless)
2a.	Efforts to be made to calm the baby
2b.	Knee to chest (by helping the parent to hold over the shoulder with knees bent with supplemental oxygen)/squatting position in older infant – (Benefits: It increases systemic resistance and also improves venous return)
3.	Sedation (intramuscular or intravenous morphine 0.1 mg/kg) (decreases catecholamine surge, heart rate and respiratory rate)
4.	Volume expansion: Normal saline (crystalloid) fluid bolus: 10–20 mL/kg by rapid IV push Augments preload and to be given prior to the following drugs which may induce hypotension
5.	Persistent cyanosis: Administration of phenylephrine 5–20 µg/kg/dose or norepinephrine infusion 0.05–2 µg/kg/min agents to increase systemic resistance and reduce the right-to-left shunt
6.	Persistence of cyanosis: IV beta-blockers—esmolol infusion 50–300 µg/kg/min or propranolol 0.1 mg/kg dose ultrashort-acting cardioselective beta-blocker (reduces dynamic muscular RVOT stenosis and increases PBF)
7.	No response with deterioration in saturation: Intubation and ventilation with correction of electrolyte disturbances and metabolic acidosis
8.	Emergency systemic to pulmonary shunt or even extracorporeal circulation (ECMO) support is occasionally indicated for refractory hypercyanotic spells

Abbreviations: RVOT, right ventricular outflow tract; PBF, pulmonary blood flow.

Table 3 Causes of heart failure according to age of presentation

First day within few hours after birth	<ul style="list-style-type: none"> Mostly noncardiac causes such as myocardial dysfunction secondary to severe asphyxia, hypocalcemia, hypoglycemia, severe anemia <i>Cardiac causes:</i> Severe tricuspid regurgitation, Ebstein's anomaly, severe ventricular outflow obstructive lesions, HLHS, large left to right shunts in preterms, arrhythmias such as SVT and complete heart block
First week	HLHS, TGA, coarctation of aorta, systemic A-V fistulas, thyrotoxicosis in newborns, a few inherited metabolic cardiomyopathies such as Pompe's disease; plus causes mentioned earlier
1 week to 1 month	Coarctation of aorta, TGA, large left to right shunts such as PDA, VSD (especially in preterms), systemic A-V fistulas, TAPVC (obstructive truncus arteriosus), SVT, endomyocardial fibroelastosis, metabolic, inherited and acquired cardiomyopathies including myocarditis, acute cor pulmonale, fluid overload syndromes
1–3 months	TGA, TAPVC, truncus arteriosus, coarctation of aorta, others as earlier
3–6 months	Large left to right shunts such as PDA, VSD; systemic A-V fistulas SVT, endomyocardial fibroelastosis, metabolic, inherited and acquired cardiomyopathies including myocarditis, TGA, TAPVC, truncus arteriosus
Beyond 6 months	Large left to right shunts such as PDA, VSD; systemic A-V fistulas SVT, endomyocardial fibroelastosis, metabolic, inherited and acquired cardiomyopathies including myocarditis, pulmonary venous anomalies, TAPVC, truncus arteriosus

Abbreviations: HLHS, hypoplastic left heart syndrome; PDA, patent ductus arteriosus; TGA, d-transposition of the great arteries; TAPVC, total anomalous pulmonary venous return; VSD, ventricular septal defect; SVT, supraventricular tachycardia.

Table 4 Basic principles of treatment of congestive heart failure

<i>Drugs selected in the treatment of congestive heart failure in children</i>	
Diuretics	Furosemide 1 mg/kg/dose (usual dose) IV or oral either twice a day or often as q 6h Spironolactone 1 mg/kg/dose twice a day
ACE inhibitors	Captopril, enalapril
<i>Inotropes to increase myocardial contractile efficiency: Digitalis and nondigitalis inotropic agents</i>	
Digoxin	Commonly used inotropic drug in the past, but now judiciously used with availability of other alternative drugs
Dopamine	5–10 µg/kg/min or epinephrine 0.03–0.1 µg/kg/min
Amrinone Milrinone Levosimendan	Phosphodiesterase inhibitors used as inotropes 0.3–1 µg/kg/min infusion with or without loading dose; 30–40 times more potent than amrinone Extremely promising new drug being increasingly used and evaluated in young children
<i>Beta-blockers therapy</i>	
Prostaglandin E1 (PGE1)	Neonates with ductal dependent systemic perfusion [0.05–0.1 µg/kg/min (effective lowest dose) up to 0.4 µg/min in unresponsive cases] See earlier
L-Carnitine	
General supportive measures	Respiratory support as needed Correct acidosis or metabolic derangements and maintain normal electrolytes Treatment of infections Treatment of anemia or other coexisting risk factors
Other options in refractory CHF due to significant cardiac dysfunctional states	
LVA devices	Increasing use of this significant advance in management of refractory failure due to systemic cardiac dysfunction and prevention of sudden cardiac death
IABP ECMO	Pre- and postoperative preparatory stages in certain CHDs and AHDs: Extensively used prior to major complex cardiac surgeries such as heart transplantation
Ventricular assist devices	Still under investigative consideration in children as an alternative to transplantation or a preparatory option
<ul style="list-style-type: none"> Cardiac resynchronization with biventricular pacing as an emergency therapy in chronic refractory CHF Implantable cardiac defibrillator—Considered in those surviving sudden cardiac arrest; programmed to respond when the heart rate goes beyond a certain preset rate 	
Cardiac transplantation	Cardiomyopathies refractory to medical and other supportive measures; mainly in dilated cardiomyopathy, others such as restrictive, hypertrophic, arrhythmogenic RV, dysplastic cardiomyopathies
Appropriate definitive surgical management as indicated in refractory cases after functional and hemodynamic stabilization with measures mentioned earlier.	

Abbreviations: LVA devices, left ventricular assist devices; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; CHDs, congenital heart diseases; AHDs, acquired heart diseases; ACE, angiotensin converting enzyme; CHF, congestive heart failure.

Myocarditis, Dilated Cardiomyopathy, Hypertrophic Cardiomyopathy and other Metabolic Myocardial Dysfunction Syndromes

Initial supportive and aggressive heart failure therapy is required. Appropriate specific therapy and timely mechanical circulatory support may be necessary to support and sustain till transplantation or recovery.

CARDIAC TAMPONADE

Cardiac tamponade is life-threatening, slow or rapid compression of the heart due to the pericardial accumulation of fluid, pus, blood, clots or gas, as a result of effusion, trauma, or rupture of the heart. Because the causes of pericardial disease and thus of tamponade are diverse, clinicians must be aware of the problem and the diagnosis. Tamponade is not uncommon in postoperative period. Pericardial effusion is the major cause of tamponade. The primary abnormality is rapid or slow compression of all cardiac chambers as a result of increasing intrapericardial pressure. Clinical features of tamponade vary, depending on the cause and rate of accumulation. They are usually tachycardic and a key diagnostic clinical finding, pulsus paradoxus, conventionally defined as an inspiratory systolic arterial blood pressure fall of 10 mm Hg or more during normal breathing is often palpable in proximal arteries (e.g., brachial). Chest X-ray shows cardiomegaly. ECG shows sinus tachycardia and low QRS voltages. Doppler echo is diagnostic. Management consists of maintaining the intravascular volume and avoiding excessive diuresis. Specific treatment is drainage of the pericardial fluid by needle pericardiocentesis or surgical drainage.

KAWASAKI DISEASE AS EMERGENCY

Kawasaki disease does not usually present as a critical emergency; however, during the acute phase of the disease, in addition to coronary arteritis, pericarditis, myocarditis, and valvar heart disease can develop. Myocarditis can lead to myocardial dysfunction and children can present hypotensive and in cardiogenic shock. Arrhythmias can be associated as well as PR prolongation and nonspecific ST and T wave changes noted on ECG. Specific treatment consists of intravenous immunoglobulin (IVIG) and high dose aspirin.

ARRHYTHMIAS

Supraventricular tachycardia (SVT) is the most frequent arrhythmia in the neonatal period and childhood in children with structurally normal hearts. Further details of arrhythmias and management have been already discussed in a separate chapter in this section.

IN A NUTSHELL

1. Patients with significant congenital heart disease present in the first few days and weeks after birth with signs and symptoms of cyanosis, shock, congestive heart failure or significant murmur.
2. The two most important presentations of life-threatening neonatal cardiac emergencies are: onset of acute hypoxemia after 24 hours of birth manifesting clinically as worsening cyanosis and shock.
3. Onset of acute hypoxemia after 24 hours of birth manifesting clinically as worsening cyanosis and acidosis suggests a right outflow tract obstruction.
4. Shock like state with feeble pulses, poor peripheral circulation, acidosis and decreased activity and responsiveness suggests a left outflow tract obstruction.
5. Prostaglandin infusion can be life-saving in both these situations as these lesions are mostly ductus dependent.

MORE ON THIS TOPIC

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Chapter 40.39

Surgical Considerations in Congenital Heart Diseases

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The incidence of congenital heart disease (CHD) has shown a very slow increasing trend over the last century. In the last 20 years, the results of treatment and cardiac surgery have become sufficiently reliable, affordable and safer option that more children have access to total correction. Major types of surgeries for CHD are listed in **Table 1**.

PALLIATIVE PROCEDURES

Palliative shunt procedures to increase the pulmonary blood flow are outlined in **Table 2**. Modified Blalock-Taussig (BT) shunt is a temporary initial palliative anastomotic procedure of shunting of subclavian arterial blood to the pulmonary artery to augment pulmonary blood flow in neonates. With the advent of better neonatal results, the indications for a modified BT shunt are becoming fewer. In comparison to the BT shunt (which acts as a left to right shunt) that increases volume load to the systemic ventricle and can cause unwanted dilatation, the Glenn shunt reduces the blood that reaches the ventricles by diverting a significant quantity to the pulmonary circulation. The success of this operation depends on good size pulmonary arteries and low pulmonary artery (PA) pressures (<15 mm Hg).

Fontan Procedure

A univentricular Fontan repair is the procedure for all cyanotic children with cardiac malformations with a single functional ventricle (in the absence of either an adequate atrioventricular valve or pumping chamber and without any possibility of two ventricular repair). Indications include tricuspid atresia, pulmonary atresia with intact ventricular septum, double inlet ventricle, hypoplastic left heart syndrome and in other complex CHDs with high surgical risk morbidity.

Children with earlier bidirectional Glenn shunt (BDGS) palliation remain well palliated for 4–5 years. When the child grows up and outgrows the quantity of blood that returns from the upper body in a reasonably well done BDGS, the need for additional pulmonary blood flow (PBF) is met by a palliative extracardiac Fontan operation. This diverts inferior vena cava (IVC) blood to the lungs by placement of an extracardiac 18–22 mm diameter PTFE conduit (polytetrafluoroethylene) independent of right heart contractions. The most important determinants of success are ventricular function and pulmonary vascular resistance (PVR).

Pulmonary Artery Banding

In children who have a cardiac lesion with increased PBF and cannot be corrected without risk as in very tiny babies, banding of the PA is a technique of reducing the PBF and protecting the lungs from increased blood pressure (pulmonary arterial hypertension [PAH]). The indications for PA banding are becoming less with increased success in corrective operations. This includes Swiss cheese ventricular septal defect (VSD), single ventricle with increased PBF and training a regressed left ventricle (LV) for arterial switch operation (ASO). The PA band reduces pulmonary pressures over a period of time to less than 15 mm Hg, this prepares the pulmonary circulation to accept a BDGS.

Table 1 Surgeries in congenital heart disease (CHD)

Corrective surgeries	Postsurgical residual issues	None	ASD, VSD, PDA, AP window TOF repair (without pulmonary valvotomy)
		Possible	Repair of AV canal, TAPVC, CoA, arterial switch operation
		Often present	Repair of TOF with pulmonary patch, placement of Conduit, Senning operation
Palliative surgeries	Early life saving, complication preventing first step procedure prior to undertaking total or near total corrective surgery later		Modified Blalock-Taussig shunt (BT Shunt) Bidirectional Glenn shunt (BDGS) Fontan procedure Pulmonary artery banding
Neonatal surgeries	Conditions		
	Ductus dependent PBF	Modified BT shunt for neonatal tetralogy, pulmonary atresia, single ventricle with reduced pulmonary blood flow	
	Ductus dependent SBF	Repair CoA, arch interruption	
	D-TGA TAPVC	Arterial switch operation (ASO) TAPVC repair	

Abbreviations: ASD, atrial septal defect; VSD, ventricular septal defect; PDA, patent ductus arteriosus; TOF, tetralogy of Fallot; AP, aortopulmonary; AV, atrioventricular; CoA, coarctation of the aorta; TAPVC, total anomalous pulmonary venous connection; PBF, pulmonary blood flow; D-TGA, D-transposition of the great arteries; SBF, systemic blood flow.

Table 2 Palliative surgeries

Palliative shunt procedures to increase the pulmonary blood flow		
Blalock-Thomas-Taussig (BTS)	End-to-end anastomosis between the SCA and PA	
Modified BTS	Use of prosthetic graft	Creation of anastomosis between subclavian artery and pulmonary artery
Bidirectional Glenn	Ligation of SVC at its entrance to RA; end-to-side anastomosis between SVC and right PA with ligation of azygos vein	

Abbreviations: SCA, systemic collateral artery; PA, pulmonary artery; SVC, superior vena cava; RA, right atrium.

SURGERY OF CYANOTIC CONGENITAL HEART DISEASE

Transposition of Great Arteries

The definitive repair for transposition of great arteries (TGA) is usually the total arterial switch procedure (Jatene) replacing the previously done Mustard/Sennings atrial switch which had long-term complications. The current mortality after corrective surgery is between 2% and 5% in the best cardiosurgical centers. **Table 3** gives the evolution of surgical palliation and corrective surgical techniques employed in TGA. Total arterial switch procedure is most successful when done under 2 week of age. In the presence of a large unrestrictive VSD, the corrective surgery is delayed as the LV is conditioned to pump against systemic pressure and resistance. Rastelli procedure is done in TGA complicated by valvar pulmonary stenosis (PS) or left ventricular outflow tract (LVOT) obstruction with VSD, and it involves closure of VSD to the aorta with conduit placed between right ventricle (RV) and PA.

Total Anomalous Pulmonary Venous Connection

The diagnosis is an indication for surgery. Obstructed type of total anomalous pulmonary venous connection (TAPVC) is a surgical emergency. Postoperative results are very good and therefore there is no need to wait, if unoperated. 99% would die within 1 year. Surgery is an open heart operation through a sternotomy, where the pulmonary venous confluence is reanastomosed to the posterior wall of the left atrium.

The mortality of elective surgery of nonobstructed type of TAPVC has been less than 5% in nonobstructive type but the perioperative mortality in obstructed TAPVC may be as high as 20% depending upon the delay in recognition.

Tetralogy of Fallot

The size of the pulmonary annulus will dictate the plan of correction. The branch pulmonary arteries are another determinant to planning repair. If they are good sized, then it is possible to close the VSD and open the pulmonary valve to achieve a complete correction. If not, use of a systemic to pulmonary shunt viz., BT shunt is essential to overcome cyanosis with additional source of blood flow.

Table 3 Transposition of great arteries: palliative and definitive corrective surgeries

<i>Transposition of great arteries (TGA)—Successive modifications in surgical approach (from early palliation to total correction)</i>	
Palliative procedures	
Creation of an atrial septal defect to allow adequate mixing of oxygenated and deoxygenated blood to allow the survival of the infants and neonates for a later corrective surgical procedure	
Blalock-Hanlon procedure	Surgical atrial septostomy
Rashkind's balloon atrial septostomy	Nonsurgical—Miller
Definitive corrective procedures by baffle atrial switch	
Correction of TGA at atrial level employing diversional baffle partitioning the atria so as to direct systemic caval blood to the left atrium and mitral valve into the subpulmonic left-sided ventricle and directing the pulmonary venous blood through the subsystemic right-sided ventricle	
Senning	Use of interatrial baffle designed by cutting and folding of the native atrial tissue
Mustard	Use of atrial baffle created by using Dacron or pericardial grafts
Disadvantages	
Despite initial reported success in long-term survival rates: Long-term baffle related complications, such as sick sinus syndrome, atrial arrhythmias, sudden deaths, progressive tricuspid regurgitation, right ventricular dysfunction and pulmonary hypertension	
Definitive anatomical and physiologic correction of TGA by arterial double switch procedures (switching aorta and main PA)	
Jatene switch	Anatomic corrective operative switch of the transposed great arteries in infants with D-loop TGA to make the left ventricle function as the systemic arterial ventricle Aorta and pulmonary arteries transected, contraposed and anastomosed with reanastomosis of left and right coronary arteries with aortic buttons to the adjacent PA designated to form the neo-aorta
LeCompte maneuver	Used in Jatene procedure to minimize coronary artery kinking
Correction of TGA with VSD and LVOT obstruction	
Rastelli 1969	Sew off main PA; external conduit from right atrium to main PA; baffle directs flow from left ventricle through VSD and out the aorta
Correction of TGA with hypoplastic RV and CHDs sharing similar functional anatomy, e.g., PA arising from dominant LV with aorta arising from rudimentary RV, e.g., tricuspid atresia with TGA, double inlet LV	
Damus-Kaye-Stansel (DKS) Procedure (Initially intended for TGA with VSD)	
Surgical steps of DKS	<ul style="list-style-type: none"> • Division of PA just proximal to its bifurcation; • Creation of tension free end to side PA to aortic anastomosis to bypass systemic outflow obstruction using a prosthetic tube connecting the severed proximal end of PA to the left side of aorta; • Restoration of pulmonary blood flow by: <ul style="list-style-type: none"> – Placement of extracardiac conduit from RV to the distal segment of dissected PA (original DKS procedure) or – As currently done shunt procedures such as: <ul style="list-style-type: none"> - Modified BT shunt mostly in neonates, - BDG (bidirectional Glenn) shunt or extracardiac Fontan procedure in older patients
Result	Early mortality in DKS: 20%
Other problems	Mild pulmonary valve regurgitation (25%); aorta-PA anastomosis narrowing—rare

Abbreviations: LVOT, left ventricular outflow tract; VSD, ventricular septal defect.

Most children are diagnosed soon after birth. If cyanosis is not severe and child is developing and thriving well without cyanotic spell, surgical repair is done between 6 months and 12 months of age. The mortality of surgery of tetralogy of Fallot (TOF) is now about 2–3 %. The surgery involves: (1) patch closure of VSD; (2) resection of RV outflow muscle bundle with or without pulmonary valvotomy or transpulmonary valve annular patch. In the presence of hypoplastic branch of PA, a BT shunt is initially done as a palliative procedure and total correction is done later.

Hypoplastic Left Heart Syndrome

Norwood procedure (3-staged operative procedures in series performed in infants with hypoplastic left heart syndrome [HLHS] to create Fontan circulation) is described in **Table 4**.

LEFT TO RIGHT SHUNTS

Patent Ductus Arteriosus

Indications for Surgical Closure in Patent Ductus Arteriosus

- Endarteritis (50% of deaths in untreated PDA)
- Left atrial or left ventricular enlargement indicating left ventricular volume overload
- PAH or the presence of left-to-right shunting
- PDAs:
 - Calcified
 - Too large for device closure, or
 - Distorted anatomy.

Asymptomatic patients with a PDA are also candidates for closure with a transcatheter device.

Contraindication for Closure

Irreversible pulmonary hypertension with right-to-left shunt.

Timing of Closure

Early closure before 6 months—large/moderate PDA with congestive heart failure (CHF), PAH or with failure to thrive. In infants more than 6 months of age, older and bigger children—a transcatheter device closure/coil occlusion or surgical ligation is done.

Percutaneous Transcatheter Device Closure

There have been many new generations of devices, including improved sheaths and sizes. The Amplatzer PDA occluder can close defects 4–12 mm in size, but smaller residual defects can be occluded with coils. New advances have also provided allowance of confirmation before device release. Temporary test occlusion with a balloon catheter can help with sizing and predict the degree of success. It decreases endocarditis, arrhythmias, and development of pulmonary hypertension. Complications and limitations include residual left to right shunt, incomplete closure, hemolysis, distal embolization, and endocarditis.

Atrial Septal Defect (other than Primum)

Many atrial septal defect (ASDs) are now closed by placement of appropriate sized sandwich occlusive devices such as Amplatzer thus avoiding open heart surgery.

Indications for Surgical or Nonsurgical Device Closure

Atrial septal defect with RV volume overload.

Age of Surgery

Surgical closure for secundum type of ASD is resorted to in children between 2 years and 4 years and it is delayed till 4–5 years of age in sinus venosus defects. Surgical closure earlier than 2 years is undertaken in those rare symptomatic infants at risk of developing pulmonary arterial hypertension (PVR >10 units/m²—contraindication for surgery) often accounting for less than 8% of ASDs, who show evidence of RV volume overload with frequent lower respiratory infections and failure to thrive; and after effectively controlling heart failure and excluding associated defects such as total or partial anomalous venous drainage, aortopulmonary window or LVOT. Surgical mortality is zero. The risk of surgery does not increase with age. However, the operated children must be followed up for years as an occasional child may develop sick sinus syndrome which may necessitate antiarrhythmic treatment or placement of a pacemaker.

Ventricular Septal Defect

Most children with large VSD are diagnosed soon after birth and can have surgical closure after 6 weeks, as the risk of PAH is not changed until this time. Waiting longer in large VSDs is not advisable. Small and moderate ones with no PAH can be kept on observation.

Indications for Surgical Closure

- Moderate to large VSD with uncontrolled CHF; recurrent lower respiratory tract infections or growth failure, markedly enlarged LV in moderate-sized defects (early infancy: 3–6 months); older children with large left to right shunt more than 2:1
- VSDs with near systemic pressures in the RV and PA
- Qp:Qs of 1.5:1–2:1
- Moderate VSD with PA systolic pressure 50–66% of systemic arterial pressure (1–2 years of age)
- Evidence of increased pulmonary arteriolar resistance is an indication for closure (PVR < 8 Wood units with a Qp:Qs > 1.5)
- A drop in PVR to levels less than 8 units after administering oxygen or other vasodilator agents, the patient becomes a candidate for surgery
- Small outlet perimembranous or doubly committed VSDs with associated aortic valve prolapse—early repair (2–3 years of age) to prevent progression of aortic insufficiency after 1–2 yearly follow-up; small VSD with any degree of aortic regurgitation—surgery, whenever AR is detected
- Small VSD with history of infective endocarditis.

Table 4 Norwood procedure (3-staged) for hypoplastic left heart syndrome

Stage I—Objectives	Limitation of pulmonary blood flow Making right ventricle the systemic pump and Ensure interatrial connection
Steps	Division of PA and creation of modified BT shunt or Sano modification; creation of neo-aorta by using PA root as homograft; creation of ASD
Stage II—Objectives	Initiation of separate pulmonary and systemic arterial circulation
Steps	Removal of modified BT shunt and creation of either BDGS or hemi-Fontan
Stage III	Complete separation of pulmonary and systemic arterial circulation

Abbreviations: BT shunt, Blalock-Taussig shunt; ASD, atrial septal defect; BDGS, bidirectional Glenn shunt.

Majority of perimembranous and inlet VSDs are closed via transatrial approach while doubly committed or subpulmonary VSD are best approached via PA under cardiopulmonary bypass. Although majority of VSDs can be dealt with surgical closure, there are situations where surgical closure is not feasible and hence PA banding is done in those situations. Mortality of open-heart VSD surgery has been less than 1% for several years in most centers.

Indications of Pulmonary Artery Banding

Pulmonary artery band procedure as a palliative may be required in the following defects refractory to medical management: multiple *Swiss cheese* VSDs with presence of some remote large muscular VSD, large VSD with straddling AV-valve, and extremely small infants.

Disadvantages of PA banding include early operative mortality, need for two surgeries, subaortic stenosis and technical difficulty involving debanding at time of second surgery.

Catheter Device Closure

Some VSDs are now closed with devices avoiding surgery but it is still in the investigational and evaluation stage in selected centers.

OBSTRUCTIVE LESIONS

Coarctation of Aorta

Intervention is not indicated in children with coarctation of aorta (CoA), if Doppler gradient across coarct segment is less than 20 mm Hg with normal left ventricular function; in all the other children with CoA and a Doppler gradient across coarctation segment less than 20 mm Hg, surgical or catheter intervention is indicated. If mild failure is present, the repair is delayed beyond 3–6 months of age. But in presence of severe cardiac failure, no delay in repair is acceptable.

Timing of Intervention

If repair of CoA is not undertaken before infancy, the incidence of hypertension increases with the time of delay. If repair of CoA is undertaken before 3 months of age, the frequency of restenosis increases. Immediate intervention is warranted in early infancy in presence of left ventricular dysfunction/CHF or severe upper limb hypertension. Surgery is performed beyond 3–6 months of age in mild upper limb hypertension with normal left ventricular function and absence of CHF. In uncomplicated children, intervention can be taken up at 1–2 years of age.

Mode of Intervention

Surgical repair involves resection of involved segment with end-to-end anastomosis, aortoplasty either with prosthetic patch or subclavian flap (Waldhausen repair) or bypass graft placement and is preferred in neonates and infants less than 6 months of age.

The operation is a closed heart surgery, which is done through a thoracotomy. It is very rare to have a coarctation on the right side, which needs a right thoracotomy. There is often a PDA that needs to be ligated at the time of coarctation repair. There is a definitive incidence of recoarctation of 5–10% and this can be treated by balloon dilatation on the second instance.

Percutaneous transcatheter balloon dilatation as a less invasive option is nowadays preferred to surgery for children more than 6 months of age with discrete CoA. Stent placement of appropriate length reduces the incidence of restenosis. Balloon dilatation with stent deployment can be considered in children more than 10 years of age, if required; currently, elective endovascular stenting of aorta is contraindicated for children less than 10 years of age.

Pulmonary Valve Stenosis

- *Mild PS* (gradient < 50 mm Hg): No intervention, only regular follow-up for increasing severity.
- *Moderate PS* (gradient between 50 mm Hg and 79 mm Hg) and *Severe PS* (> 80 mm Hg): Balloon or surgical intervention after stabilization and treatment of CHF.
- *Dysplastic PV with severe PS* in children—surgical valvotomy.

Aortic Valve Stenosis

- *Mild AS* (gradient < 25 mm Hg): No intervention only regular follow-up for increasing severity.
- *Moderate AS* (gradient between 25 mm Hg and 50 mm Hg): No intervention only regular follow-up for increasing severity.
- *Severe AS* (> 50 mm Hg gradient with symptoms or a peak gradient of 70 mm Hg): Balloon intervention is the preferred and rewarding intervention with surgical intervention is resorted to AS with aortic regurgitation or for those with unsuccessful balloon valvuloplasty.

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Chapter 40.40

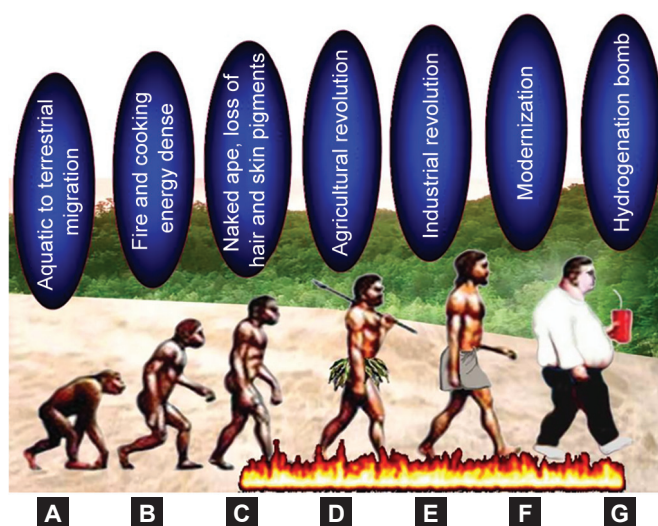
Preventive Cardiology in the Young

S Sivasankaran

Antagonistic pleiotropic theory of aging typically identifies fitness and reproductive success as the prominent life history traits which are achieved at peak adolescence followed by aging and age related disorders. Hence, adolescence is the last opportunity to achieve best cardiovascular health to invest in healthy aging. The Special Turku Coronary Risk Factor Intervention Project (STRIP) study, which evaluated the benefits of lifestyle interventions from weaning, now, forms the scientific foundation for the preventive strategies from infancy.

EVOLUTIONARY FOUNDATION FOR LIFESTYLE INTERVENTIONS

Figure 1 pictorially summarizes the various landmarks in the evolution of human lifestyle.



Figures 1A to G Major landmarks in the evolution of human lifestyle and dietary pattern: (A) Aquatic to terrestrial migration characterized by the evolution of increasing peripheral vascular resistance, the vitamins (C and D) antioxidants and incretin system; (B) Forest fires providing energy dense food makes cooking an integral part of human life; (C) Migration to temperate climate with loss of skin pigmentation; (D) *Agricultural revolution*: Dried seeds (cereals, pulses, nuts and tubers) provided a storage option to overcome famine. Domestication of animals and birds substituted game meat by poultry meat and dairy products; (E) Industrial revolution lead to extraction of salt from sea, sugar from sugar cane, oil from oil seed, and alcohol from fruits, for which human body is least adapted; (F) Modernization provided these energy dense foods in supersizes and feasts whereas the energy needs steadily declined at least by a factor of 5. Stress and tobacco use aggravates the noncommunicable disease epidemic; (G) Hydrogenation bomb refers to the industry mediated popularization of trans-fats along with marketed products, rich in salt, sugar, fat, colors and preservatives, with minimal dietary fiber, and nutrients

(Photo Courtesy: Ms Vasanthy)

The evolutionary biological adaptations to the present human life style can be traced back to major events starting with the aquatic to terrestrial migration of amphibians. The major physiological challenges the animal kingdom faced on this transition were that of gravity and oxidant stress. This necessitated the evolution of many adaptive mechanisms such as the antioxidant systems and antigravity adaptations.

Antigravity Adaptations and Antioxidant System

Loss of buoyancy increases the body weight on aquatic to terrestrial migration. This six-fold increase in body weight necessitated increased peripheral vascular resistance in systemic circulation and higher blood pressure to perfuse tissues and to maintain an optimal perfusion pressure to the cephalad located blood hungry organ, the brain. This is achieved by the further adaptation of the renin-angiotensin aldosterone system and ability to taste salt. Separation of the pulmonary to systemic circulation helped to maintain lower pressure in the pulmonary circuit and made the system more efficient. Evolution of the sunshine vitamin (vitamin D) and its nuclear receptors and healthy, less heavy hollow bones, can be identified as the next landmark. Efficient antioxidant systems helped the animals survive the oxidant stress when the oxygen content increased from 0.5% in water to 20% in the atmosphere. The coevolution of color vision and colored fruits in the plant kingdom facilitated the disappearance of vitamin C synthetic mechanism in primates making them dependent on nutrition for their antioxidant needs. James Lind is credited for the first dietary intervention studies when he saved the life of sailors by providing them with citrus fruits centuries before the discovery of vitamin C. No wonder colored fruits and vegetables are recommended to form half the dietary plate in the current recommendations.

Polar Migration and the Sunshine Deficit

Migration of humans/primates from the equatorial zone towards temperate climate generated fair skin which potentiated vitamin D synthesis by five times making human survival possible at extremes. Epidemiological studies in India have identified vitamin A, vitamin C and vitamin D deficiency to the order of 75% in various segments of the population including children. Studies on vitamin D, vitamin C and antioxidant substitution in adults have not shown any survival benefits. Best bones are achieved at peak adolescence and later supplementation only tries to reduce the rate of bone loss. Indians because of their dark skin synthesize five times less vitamin D and adolescent girls need five times more vitamin D to meet the pregnancy demands. Low maternal vitamin D level correlates with early onset of noncommunicable diseases in the offspring. Providing vitamin D alone is not enough, we need exercise to stimulate the bone growth. Hence, childhood and adolescence is the last opportunity to develop healthy bones as an investment for healthy old age.

Physical Activity

Skeletal muscle is ten times more insulin sensitive compared to adipose tissue and good physical activity is the best way to minimize the onslaught of hyperinsulinemia generated by adipose tissue insulin resistance. Thus, nutrient mediated (insulinogenic) growth predominantly favors adipose tissue growth whereas physical activity (growth hormone) mediated growth builds good muscles and bones. Both isotonic exercise and isometric exercise to lift one's own body weight is essential. Swimming in water can be identified as the most physiologically optimal exercise, avoiding the body weight induced damage to joints. Water provides a good medium for cooling the body and swimming activates both axial and appendicular muscles. Next best place for physical activity

could be the sandy beaches. Gentle breeze keeps the body cool and provides a good resistance for movement. The soft sand acts as the shock absorber to the stress on the joints on walking and jogging.

Traditional Cooking

Provision of energy dense, easily digestible food substances rich in omega-3 fats is considered to be the major factor for primate brain evolution. The shorter gastrointestinal tract of humans mandates cooking as an unavoidable necessity for survival. Good traditional cooking makes food palatable, digestible and nutrient rich. Deep frying destroys the heat sensitive vitamins, polyunsaturated fats and oxidizes the lipid components. Clarified butter (*Ghee*) was demonstrated to be atherogenic because of these oxidation products and hence no longer recommended in diets. Over the last 10,000 years human civilizations flourished, and farming and agriculture evolved as major society achievements. The biological adaptations which evolved slowly further got shattered by the industrial revolutions over the last 200 years.

Agriculture and Poultry Farming

Initiation of agriculture facilitated the use of energy dense pulses, cereals, millets, tubers facilitating social life and efforts to overcome famine. Hydrating these dried seeds during traditional cooking made these products less energy dense. Domesticating animals and poultry farming were the next major dietary changes experienced by *Homo sapiens*. Milk is essentially the secretion from the mammary gland meant for lactation in mammals and the ability to digest lactose is lost at the end of weaning. Human beings modified this genetic programming by repeatedly exposing himself to milk so that now 85% of the population is lactose tolerant. Thus milk and egg along with other animal sources enriched the diet with cholesterol and cholesterol generators. Ancel Keys in his landmark seven country study demonstrated 14-fold increase in cardiovascular mortality as population cholesterol increased from 200 mg/dL to 240 mg/dL. Finland was the first country to embark a comprehensive lifestyle program where people shifted from poultry farming to berry cultivation. Finland was the heart disease capital for the world in 1973 achieved a steady decline in cardiovascular mortality to the tune of 80% by 2007. One of the notable achievements was that the percentage of people using butter along with bread declined from 95% to 5% with a corresponding decline in blood cholesterol levels. Similar decline per capita salt consumption and tobacco use and increasing physical activity were major achievements. Human dietary pattern is omnivorous, but biology is more herbivorous as evidenced by our dependency on vegetable sources for vitamin C and dietary sensitivity to cholesterol. Cholesterol is the steroid for the animal kingdom compared to ergosterols and sitosterols of the plant kingdom. Herbivorous animals can synthesize their need for cholesterol and hence adult humans have an upper limit for their daily cholesterol intake as 200 mg. Poultry farming further changed the dietary pattern from game red meat to fat rich poultry meat. Ordinary egg yolk provides 300 mg cholesterol and a double omelet provides three times the recommended adult dose to a child. Fermentation provided various probiotics and tasty menus, but generation of alcoholic beverages evolved as health menace to mankind.

Insulinogenic Nutrition

It refers to consumption of energy dense food substances and declining physical activity, which favors insulin mediated growth of adipose tissue, obesity and metabolic syndrome. Socialized societies no longer were predated nor faced calamities such as famine. Civilization further harnessed the natural instincts on taste to generate salt from the sea, sugar from sugar cane, oil from

oilseeds, and alcohol from fruit juices. Refining cereals deprived them of their fiber content and vitamins and made them more insulinogenic. Development of beriberi on eating polished rice was demonstrated by Eijkman decades before the discovery of vitamins. This paved the way for nutrition recommendations for the first time.

Consumption of fruit juices is considered equivalent to consumption of one serving of fruits because juicing them makes them more glycemic. Salt evolved as the favorite of the industry because of its ability to preserve food. Further the osmotic challenge induced by the salt makes one consume more sugar sweetened beverages and alcohol. In addition salt provides an acidic challenge. Body fluids contain 140 mEq of sodium and 100 mEq of chloride. Consuming sodium chloride provides equal amounts of sodium and chloride to the body and the excess of chloride provided needs to be buffered by the calcium in the bones leading to osteoporosis and renal stones in susceptible individuals. Recently, concluded HORUS study evaluated Egyptian mummies with computed tomography (CT) scan, demonstrated osteoporosis and vascular calcification in 22 out of 40 mummies below the age of 40 years making atherosclerosis an old disease. Though inflammation was discussed as a possible cause, that period in evolution of mankind corresponds with the popular use of salt by man for preservation. Salt makes the blood vessels stiff. INTERSALT study (an international study of electrolyte excretion and blood pressure) showed that all the six human population who do not use salt in cooking did not have the age-related increase in blood pressure. Naturally salt restriction will have minimum benefit once the blood vessels have stiffened and the studies on adult salt restriction are equivocal.

Fructose and alcohol provide empty calories and aggravate the insulinogenic nutrition, by glucose sparing. Sugar such as cholesterol is not an essential nutrient. Unfortunately, present day children consume five times more sugar than what is recommended, aggravating the damage arising out of insulinogenic nutrition. Though pediatric doses are the rule in pharmacology, supersizing is the rule for bakery products. Biscuits and chocolates were fiber deficient energy dense products initially packed for the soldiers, but their long shelf-life made them the favorite for the industry. Food processing at the industry level makes them more energy dense whereas traditional cooking by hydration lowers the same.

Hydrogenation Bomb

Fat and oils are energy dense cooking medium which make the food tasty and last long in the shelf. Undue frying and reheating generated various oxides and destroys the unsaturated fats and vitamins. Fat transported through chyle directly enters blood and escapes first pass metabolism and avoids incretin release. But when in excess they generate insulin resistance by altering the membrane physiology and glucose sparing such as alcohol and fructose. Trans-fats are highly atherogenic and the favorite for the industry. Long shelf life associated with trans-fats turned out to be the ultimate hydrogenation bomb for mankind. Many countries have banned trans-fats in food and introduced fat taxes to contain the obesity epidemic. Fish and fish oils are cardioprotective but they have lost their nutritive value because of the added salt during preservation and cooking. Deep frying and the bio-accumulated toxins (mercury, lead and pesticides from water) and cholesterol load associated, has made fish no longer heart friendly. Hence, currently fats and oils are recommended to be used only for seasoning which is adequate to meet the essential fatty acid/vitamin need for the body. Currently, urbanized society there is a five-fold decline in energy needs and fried foods are no longer physiological in ordinary diets. The clinical evidences for the mal-

adaptation to our evolutionary programming are represented by sarcopenia, osteopenia, adiposity and metabolic syndrome and their consequence in later life. These evolutionary principles form the sound foundation for the healthy diet plate as illustrated in **Figure 2**.

EPIDEMIOLOGICAL TRANSITION IN INDIA

Autopsy studies in India in 1950s identified atherosclerosis as an uncommon disorder prevalent in old age in India with 15% prevalence in 7th and 8th decade. Corresponding figures showed that the disease prevalence was 45% in 6th decade at Boston. Thus the disease got identified as an outcome of urbanization and westernization. The 1960 epidemiological studies at Chandigarh showed that coronary artery disease prevalence was as high as in Tecumseh in United States establishing the Indian susceptibility to urbanization and westernization.

India has witnessed a steady epidemiological and nutrition transition to evolve as the diabetes and hypertension capital for the world. Both studies on migrants and native Indians have now documented a heavy burden of cardiovascular diseases, almost twice as that of same aged individual in the United States or three times that of Japanese. The diseases occur at least a decade earlier than their counterparts. Younger age escalation of all these diseases and risk factors are documented in population studies as well as from the birth cohort studies. Follow-up data from the New Delhi Birth cohort shows that the incidence of diabetes from the age of 29 to 36 is 1% per year, obesity 2% per year and that of hypertension 4% per year. The increase in risk factors in the

adolescent men is steady whereas in women in the reproductive age group is exponential.

Three patterns of evolution of noncommunicable disease have been noted across the world. Developed countries documented a steady increase in prevalence of the disease as the population aged and with increasing body mass index reflecting gluttony and sloth as the driving forces. Developing nations showed a steeper increase in prevalence of diabetes reflecting additional factors like inflamed fat (adiposopathy) and sarcopenia (lack of skeletal muscle reflected by physical fitness) as the additional drivers. Aboriginal population such the Pima Indians, and Pacific Islanders showed much steeper curve because of the gestational diabetes. Gestational dysglycemia leads to activation of beta cells in utero and premature onset of diabetes in the offspring. The patterns seen in developing countries in India now combine factors for the second and third pattern and hence likely to be worse. Thus the behavioral risk factors in adults has transformed into in utero risk factors for Indians manifesting as gestational obesity, dysglycemia, vitamin D deficiency, hypertension and dyslipidemia and inflammation reflected by skin changes such as acanthosis nigricans. These patterns in increasing prevalence of noncommunicable diseases and risk factors are summarized in **Figure 3**.

CONCLUSION

The driving force for the younger age escalation of risk factors and diseases in India reflects the unhealthy motherhood (in utero

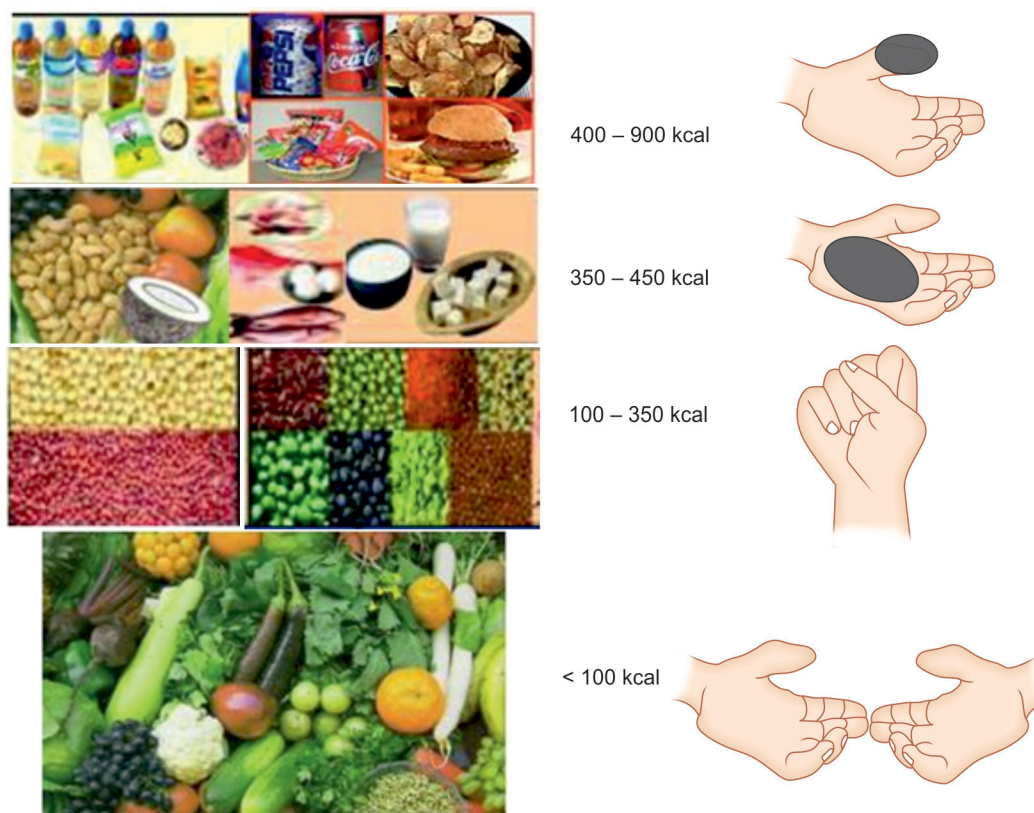


Figure 2 Scientific basis of perfecting a diet plate (kcal/100 g of food). Food substances that are most adapted could form the major plate portion; say hand full of low calorie low glycemic, food rich in dietary fiber, flavonoids and antioxidants represented by colored fruits and vegetables. More energy dense cereals and pulses are limited to hand full food portion and are to be served sprouted or traditionally cooked. More energy dense, nuts, tubers, poultry products need to be limited to a palm size food portion. A pinch of marketed food products are recommended since they are least adapted for optimal health

risk factors) achieved by the Indian girls. Insulinogenic nutrition is characterized by declining energy needs and increasing energy density and glycemia of the food consumed and is least adapted evolutionarily. Poor breakfast and a heavy dinner again reflect a dietary insult when the physical activity is least during the nocturnal sleep. The outcome is exaggerated because of the ethnic susceptibility, sarcopenia, low vitamin D levels and other issues leading to inflammation in Indians. Ecological and

epidemiological basis for the present epidemic is presented to substantiate the fact that noncommunicable disease prevention is a mother and child health priority. Every effort should be made to make children physically active in the sun, and to train them evolve a healthy diet plate for which their physiology is most adapted. **Figure 4** schematically represents the old and new nutrition cycle which drives the nutrition related diseases in India.

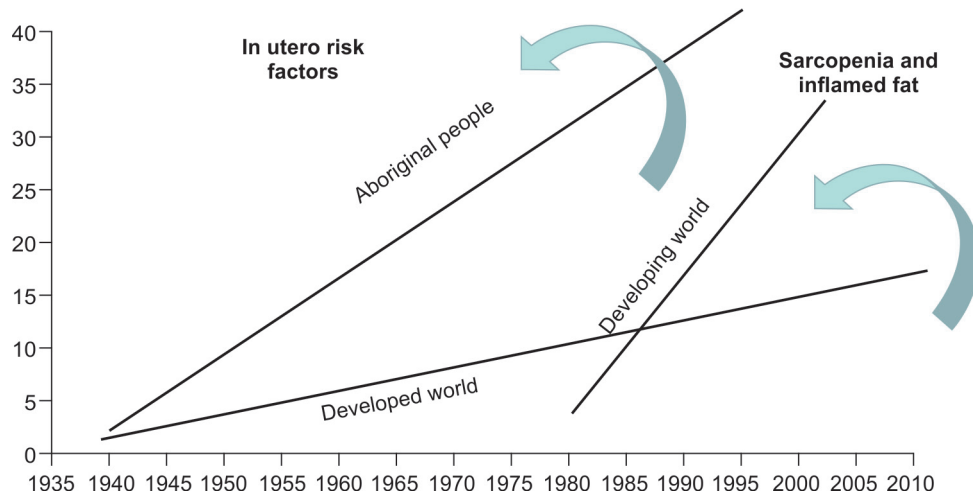


Figure 3 Three patterns in the epidemiology of noncommunicable diseases and risk factors noted in the world. The most common pattern seen in developed world is characterized by increasing prevalence of noncommunicable diseases which correlates with increasing age and body mass indices. The second pattern is seen in developing world. Here the pattern is shifted up by adiposopathy (inflamed fat) and sarcopenia, when risk factors occur at lower body mass indices and younger age. The pattern shifts further to left side as the third pattern with early onset of risk factors in offspring or children born to mothers with in utero risk factors as seen in rapidly westernizing and aboriginal population (Pima Indians, Pacific islanders, and Asian Indians) 1

Modified from: Bhattarai MD. Three patterns of rising type 2 diabetes prevalence in the world: need to widen the concept of prevention in individuals into control in the community. JNMA. 2009;48:173-9.

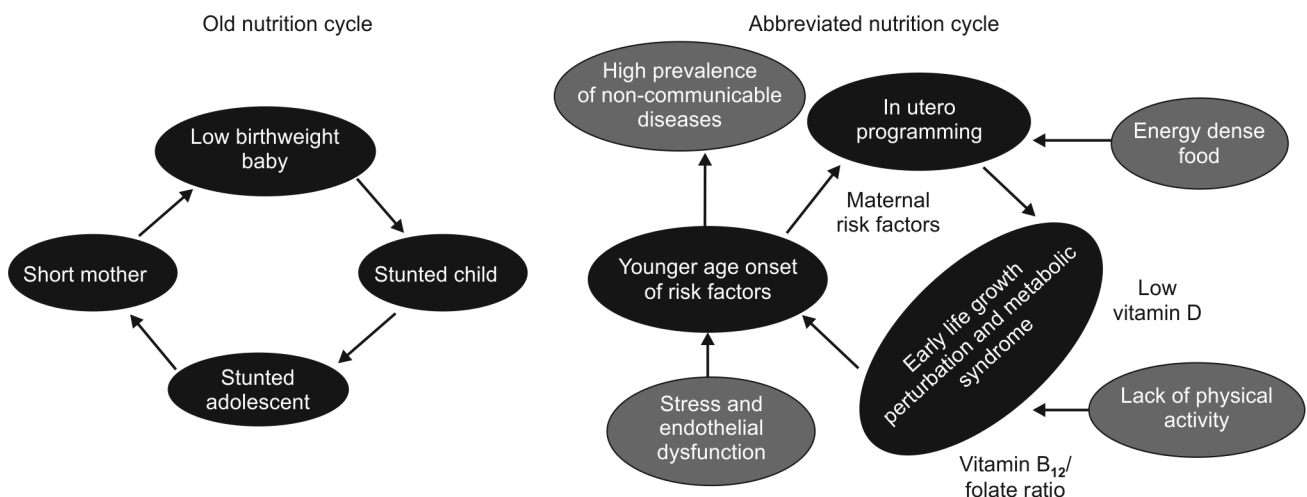


Figure 4 The nutrition cycle, old and new, depicted by the dark ovals and thin arrows. The lighter ovals and short arrows show the drivers and the dark dotted arrow leads to the final outcome. In the old nutrition cycle, vicious cycle generated by stunted mother giving rise to low birthweight baby generated the stunted adolescent and hence mother and child healthcare argued for increasing the nutritional intake to achieve better growth in childhood and adolescence. Simultaneous decline in physical activity and other factors such as low vitamin D levels generated younger age escalation of risk factors. Maternal risk factors adversely program the baby for early onset of risk factors generating the new abbreviated nutrition cycle where the onset of risk factors occur at a younger age

IN A NUTSHELL

1. Childhood and adolescence is the best opportunity to evolve a healthy body composition as an investment for healthy aging devoid of noncommunicable diseases and risk factors.
2. Physical inactivity and unhealthy diet are the major drivers of the noncommunicable disease epidemic in India in children and adolescents.
3. Osteopenia, sarcopenia (less skeletal muscle), adiposity, micronutrient deficiencies and adipocyte inflammation (adiposopathy) are important aspects which predispose the development of metabolic syndrome and noncommunicable disease risk factors.
4. Salt—a no calorie dietary product—which preserves food contributes to the age-related increase in blood pressure and also osmotic and acidic challenge to the body.
5. High increase in oxygen availability at birth necessitates an efficient antioxidant system. Human ability to see colored products is to prioritize colored fruits and vegetables in the healthy diet plate to minimize this oxidant stress.
6. Gravitational increase in body weight necessitates the increase in systemic vascular resistance and development of hollow long bones.
7. Insulin sensitivity of various tissues such as, adipose tissue, liver and skeletal muscle can be modulated by diet, drugs, hormones and physical activity.

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